THE PRACTITIONER

No. 1096 OCTOBER 1959 Volume 183

THE MONTH

ONCE again our annual Special Number devoted to 'Advances in Treatment' records a period of consolidation rather than advance. New hypotensive agents and new steroids appear with great regularity, but none of these represents any dramatic advance. To a certain extent they confuse the issue for the practitioner by presenting him with such an array of active agents that he finds it difficult to decide which to use. As more than one contributor to our Special Number points out, the sound rule is to keep to one of them so that the user comes to understand its advantages and disadvantages. It is for the consultant, with all the facilities of adequate numbers of patients, a team of fellow-workers, and laboratory facilities, to work out their relative advantages. In some ways, perhaps the most important advance from the point of view of the general practitioner is the introduction of the new oral diuretics which are not only safer than the old mercurial diuretics but so much easier to administer. Among the most widely acclaimed of advances of recent years was the introduction of the oral hypoglycæmic compounds. Inevitably, undue hopes were raised concerning their efficacy. Sufficient evidence—summarized in the article on 'Advances in Diabetes Mellitus'—has now been accumulated to show that in actual practice their use is restricted to a relatively small proportion of diabetic subjects.

The Symposium

BY tradition a doctor does not charge another doctor for his professional services. The forbearance is mutual, and usually includes the care of the whole family. Today, however, medical or surgical fees represent but a small item in the cost of sickness, and the doctor who falls ill is liable to find himself involved in heavy expense to cover the cost of nursing-home, or private-wing, fees. For those with families the liability is even higher. One of the most striking phenomena of the last decade has been the rapid expansion of insurance schemes to cover the cost of illness. Many companies, of which the British United Provident Association (B.U.P.A.) is probably the best known, now offer a comprehensive scheme that, for a modest premium, covers the cost of any illness involving specialist treatment, including nursing-home charges and specialists' fees within defined but generous limits.

'The Practitioner' and B.U.P.A.

As a development of these schemes many large firms now have a group arrangement with the insurance companies, whereby the benefits of sickness insurance are available to all their employees at a considerable reduction

in the premium. Hitherto such a 'group' arrangement has not been available for the medical profession as a whole. We have for long felt that this was a state of affairs that should be remedied. We have now come to an agreement with the British United Provident Association to set up what will be known as *The Practitioner* Group. Under the terms of this agreement, as from January 1, 1960, subscribers to *The Practitioner* will be able to register with the British United Provident Association for sickness benefit at a reduction of 20 per cent. in the standard premium for the particular policy they wish to adopt. Details of the scheme will be found on the back page of this issue, but there are two points to which we would particularly draw attention, apart from the quite considerable saving on the premium. The first is that the scheme covers the subscriber's family as well as himself. The second is that, apart from anything else, by joining the scheme the subscriber will be relieved of the often invidious task of showing his appreciation of his specialist's services without offending his susceptibilities. Under the Group scheme B.U.P.A. will, on request, send a cheque direct to the specialist, explaining that it represents benefit payable because of membership of the Association.

The Control of New Drugs

ONCE again the Council of the Pharmaceutical Society of Great Britain has issued an appeal for Governmental action to prevent the sale of tranquillizers and stimulants to the public except on medical prescription. It was three years ago that the Council issued a similar appeal but, for all practical purposes, this fell on deaf ears. The amphetamines have been placed in the Fourth Schedule and methylpentynol in the First Schedule, but there is no restriction whatsoever on the sale to the public of the tranquillizers, the open-chain ureides and some new sedatives and stimulants. It is impossible to assess the full extent of the harm being done by the uncontrolled sale of these drugs, but a member of the staff of the Maudsley Hospital has recently reported (*Lancet*, 1959, **ii**, 152) that within a period of six months he saw no fewer than sixteen patients who had taken 'preludin' and had become ill; twelve of them had a psychotic disturbance.

In these days when punitive legislation is at a premium, it is difficult to understand why those in authority refuse to take action in this matter. By their delay they are accepting a heavy responsibility. Two immediate steps are called for. One is the immediate scheduling of the twenty-seven preparations which are included in the statement issued by the Pharmaceutical Society. Equally important is the introduction of legislation forbidding the sale of any new drug to the public until it has undergone a prescribed period of clinical trial and been shown to be free of any risks. The old narrow definition of drugs of addiction is no longer adequate and, as experience has shown, the present method of scheduling drugs is much too cumbersome to be effective. Action must be taken before the drug is ever made available. Such legislation would impose no hardship on the pharma-

ceutical industry, it would not interfere with the freedom of prescription by doctors, it would protect pharmacists from their present invidious position of having to decide whether to sell a new drug to a customer, and it would provide the public with the protection to which they are entitled.

Tired-Mother Syndrome

In a series of 60 women, with at least one child under the age of 16 years, whom he saw over a period of several months, L. L. Lovshin (*Postgrad. Med.*, 1959, **26**, 48) made a diagnosis of 'tired-mother syndrome' in forty-eight. None of them was under 20 years of age, and there was no correlation with the number of children. 'Apparently', he says, 'a tired mother with one child worries four times as much, per child, as the mother with four children'. The tired-mother syndrome 'usually afflicts a worrisome, tense, overly conscientious mother who cannot quite keep up with all the tasks she has set for herself'. She begins to feel tired, run down and irritable. As the tiredness is often not relieved by a night's sleep, she soon becomes convinced that there is something seriously wrong with her. 'Her reading of medical articles in women's magazines having acquainted her with a number of major diseases, she soon is prepared to accept the fact that she has one or even several of them'.

There are several subtypes of tired mothers. One is the working mother—the woman who by necessity or choice goes out to work. Another is the older mother—around 40—who has lost her resilience. A third is the displaced-person tired mother, who is in a hurry to become Americanized—i.e. to own a car and household gadgets—and takes on an outside job as a 'cleaning lady' (charwoman in English). It is these women who lap up multivitamin preparations and nerve pills, or, if they fall into the hands of a certain type of doctor, have regular injections of vitamins (B_{12}, apparently, is the favourite at the moment in the United States). Lovshin's common-sense advice in the management of this new syndrome is typified by his concluding remarks: 'It may do no good, but it can certainly do no harm to point out to the patient that the last generation of tired mothers came through it all very well, and that now as grandmothers they think back, misty-eyed, to days long ago, and wish they could return to that period of woman's greatest productivity, those glorious days when the children were young, the demands great, the time too short—those wonderful days when they as mothers were enthusiastic, hard-working, and *very, very tired*'.

Mass Hunger Strikes

Mass hunger strikes are a phenomenon of which we in Western communities have had relatively little experience. In the East, however, they have come to the fore of recent years as a political weapon. India has probably had as much experience of them as any other country. The extent of the problem is exemplified by the fact that in a recent issue of the *Indian Medical Journal* (1959, **53**, 63) a lengthy article was devoted to the subject of 'Management of mass hunger strikes'. In this article the author, Dr. Sushil

Kumor Roy, a police medical officer in West Bengal, refers to his experiences in two such strikes—one involving 136 people who had been on hunger strike for 36 days with tube-feeding, and the other involving 238 people who had been fasting for 53 days with tube-feeding.

Among some of the interesting points brought out in his article are that old people can stand starvation better than young adults, and that women can withstand starvation for longer periods than men. This last point he attributes in part to the fact that in India women are more accustomed to religious fasting than men. So far as 'caste' is concerned, Sikhs stand up to starvation best of all, followed by Hindus, Anglo-Indians, and Muslims, in that order. In discussing prognosis the view is expressed that death is not common under ten to twelve days, even if neither food nor fluid is taken. If only food is refused, life may be prolonged for six to eight weeks if sufficient water is taken. The essence of treatment is forced tube-feeding by the intranasal route. The aim is to give the equivalent of 2000 calories daily: in two daily feeds, each containing around 1000 calories. If there are marked signs of dehydration and acidosis, intravenous glucose, with or without calcium and ascorbic acid, should be given. In more severe cases it may be necessary to give an intravenous drip of 5 per cent. glucose in saline. Maintenance of body heat is essential, and daily massaging with mustard oil, and regular bathing, are said to be of value.

'Angostura Bitters'

THE name, 'Angostura bitters', is so well known that there are probably few who have ever thought about its origin. Those who did probably assumed that they were prepared from angostura bark. Apparently this is not the case. They contain gentian as a bitter, and various aromatic ingredients, but no angostura bark. They owe their name to the town in which they were first produced. The story of this universally known preparation has recently been told in the *Pharmaceutical Journal*.

The formula was devised by Dr. J. G. B. Siegert, a German surgeon who served with the German army at Waterloo. In 1820, he migrated to Venezuela and settled in the town of Angostura on the Orinoco river. It was there that he produced the formula for his well-known 'bitters', and named it after its town of origin. It was originally intended as a medicine, but rapidly became known as a good flavouring agent—and it is in this capacity that it is now known throughout the world. Its manufacture has remained ever since in the hands of the Siegert family. In 1875, because of the troubled state of Venezuela, the manufacture of the 'bitters' was transferred from Angostura (or Ciudad Bolivar, as it is now known) to Trinidad. The bark, like the bitters, owes its name to its port of origin. It is obtained from a South American tree known as *Galipea officinalis*, or *Cusparia febrifuga*. It was first imported into England as a medicine in 1788, and was accepted in the *London Pharmacopœia* (1809). It was not until 1949 that it was omitted from the *British Pharmaceutical Codex*.

ADVANCES IN MEDICINE

By IAN G. W. HILL, C.B.E., T.D., M.B., F.R.C.P., F.R.C.P.Ed.

Honorary Physician to H.M. The Queen in Scotland;
Professor of Medicine, University of St. Andrews

A REMIT to survey the important advances in medical treatment recently introduced is a task to daunt any reviewer. Such is the pace of progress in many branches of medicine today that no one individual can hope to remain fully cognizant of all that is going on in fields other than his own specialty, and even in one field, say for example cardiology or hæmatology, it is increasingly difficult for a doctor to remain master of the diverse techniques and the complex discoveries which stem from their application. The following review makes no pretension to be either exhaustive or authoritative, but is a personal appraisal of significant novelties.

SURGICAL TREATMENT IN HEART DISEASE

Surgical treatment for certain types of rheumatic valvular disease and for some varieties of congenital cardiac malformation is now established practice, and it may be questioned why it finds a place in this review of recent advances in treatment. It is appropriate, however, some ten years after the introduction of surgical treatment, to review the results which are being obtained and the grounds on which cases are selected for submission to surgery.

Rheumatic heart disease.—In the first place, in rheumatic heart disease there is general agreement that operations for *mitral stenosis* are rewarding, both in respect of alleviation of symptoms or failure and in prolongation of life. On the other hand, operations for relief of aortic stenosis are by general consent more hazardous, both in respect of risk to life and in respect of the prospect of improvement. The mortality in properly selected cases of mitral stenosis is of the order of 2 per cent. or thereby, whilst the operative mortality in cases of aortic stenosis is at least five times as high, and on occasion still higher. Unfortunately there is as yet no generally accepted surgical procedure for the relief of patients suffering from mitral incompetence or aortic incompetence; in fact, the presence of significant regurgitation at either valve is a strong contraindication to operative treatment of stenosis of either orifice. The assessment of the degree of regurgitation at these valves is not always easy, and in any case of doubt it is wise for the practitioner to refer the patient to a specialized cardiac clinic. Even with the full resources of such a well-equipped centre errors in diagnosis are by no means uncommon, but at least every step should be taken by practitioner and specialist alike to ensure that the subjects of rheumatic heart disease are reviewed with the possibility of surgical relief in mind, and are afforded the opportunity of surgical treatment when applicable.

A point of some interest has arisen in the follow-up of patients who have been subjected to mitral valvotomy in the past. Quite a number of patients who have had such an operation have presented again in the course of three or five years with symptoms of similar intensity to those which warranted the original operation, such symptoms having developed after a period of relief which has lasted for a variable time, up to several years. Numbers of such patients have been submitted to a second operation and re-stenosis of the valve has been found—a re-stenosis which has yielded to a second valvotomy with corresponding immediate improvement in the patient's disability. That such operations should in fact prove necessary from time to time is no argument against mitral valvotomy as a primary operation, since in many instances a full measure of relief has been afforded to the subject for several years and a second operation is not unduly hazardous.

A further problem is that of the mitral stenotic who develops significant symptoms during a pregnancy and who may require consideration for valvotomy during its course. In many such women it is possible by a régime of rest and treatment to coax them through the remaining months to term without undue hazard, but in some the risks are considerable. This is particularly the case in the patient with a relatively small heart, a tight stenosis and normal cardiac rhythm, in whom attacks of acute left heart failure have occurred with paroxysmal acute dyspnœa. In such patients urgent operation on the valve is not only feasible but advisable. In my own experience a number of such patients have been treated by operation without interruption of the pregnancy, and have gone on to term to have a spontaneous delivery without failure or other complication.

The decision when to operate in those with *aortic stenosis* is always much more difficult to reach. In general, the younger the patient the lower the mortality and the less the risk of that extensive calcification which interferes with a successful result. Conversely, patients who are up in years, whose heart muscle is either grossly hypertrophied or on the verge of failure, and patients who have angina pectoris or paroxysmal dyspnœa, or, worst of all, who have had congestive failure, are bad risks. Again the final assessment as to suitability for operation should be reached in a specialized centre after consultation between surgeon and physician, and on the advice of the general practitioner who knows the home circumstances of the patient and who is able to advise regarding his environment.

Congenital heart disease.—In respect of congenital heart disease some of the simpler lesions lend themselves to immediate surgery: e.g. such conditions as patent ductus or uncomplicated Fallot's tetralogy. In other cases, particularly coarctation of the aorta and pulmonary stenosis, the decision to operate can only be taken in the light of the patient's disability together with the hæmodynamic findings as revealed by detailed investigation. So, too, in cases of atrial septal defect it may be that detailed investigation will reveal a small shunt of no hæmodynamic significance which may

well be left alone. On the other hand, patients with such defects who have large shunts should be submitted to operation in a properly equipped centre before they reach their twenties, since it is well recognized that the average patient with this lesion becomes severely disabled in the third or fourth decade. The techniques of arrested circulation under hypothermia and of artificial circulation maintained by a heart-lung pump have rendered feasible intra-cardiac operations under direct vision in the opened arrested heart, and have brought a number of malformations into surgical possibility. It is thus clear that practitioners should refer all children with suspected congenital heart disease to a specialized clinic for diagnosis and assessment.

ETIOLOGY AND MANAGEMENT OF CORONARY DISEASE

Coronary artery disease, with its twin clinical manifestations of angina pectoris and myocardial infarction, remains a most serious clinical problem, both in respect of its prevalence and in respect of the manner in which it strikes down or disables individuals in the prime of life. Surveys in America, in Europe and in South Africa have all shown a striking correlation between the social status and diet of individuals on the one hand and their susceptibility to coronary disease on the other. Further, a curious parallelism has been demonstrated between the incidence of coronary disease and the height of the blood cholesterol. In the so-called 'underdeveloped' countries, in which the diet is generally exiguous and is certainly poor in fat, the blood cholesterol runs on an average about 150 mg. per cent., whilst in the Western world with a much higher calorie intake and a much higher proportion of the total calories consumed as fat, blood cholesterol levels run from 250 to 280 mg. per cent. The incidence of coronary disease among the individuals of the underdeveloped races is negligible, and a close step-by-step correlation can be shown between the rise of the blood cholesterol with increasing richness of diet and the incidence of coronary disease, both reaching their peak in the United States, where 40 per cent. of the total calories are taken as fat, the blood cholesterol level tends to run about 280 mg. per cent., and the incidence of coronary disease is the highest in the world. Diabetics and the subjects of myxœdema, in whom high blood cholesterol figures are the rule, have a notoriously high incidence of coronary disease.

As an amplification of this work, considerable attention has been devoted to the nature of the fat in the diet and it has been shown that the *unsaturated fatty acids*, when taken in quantity, have a cholesterol-lowering effect. Such unsaturated fatty acids occur commonly in vegetable oils (from maize, sunflower seed and other sources) and in the United States particularly substitution of unsaturated for saturated fats in the diet is undertaken on a wide scale. In this country substitutes for butter and margarine and similar substitutes for cooking fat and cheese can be obtained, containing corn oil, and the ingestion of these preparations in a quantity of 50 grammes a day, in place of the conventional fats of our ordinary daily

diet, has been shown to cause a fall in the blood cholesterol. Whether a fall of blood cholesterol *per se* will induce a corresponding fall in the incidence of coronary disease is a moot point, but there would at least appear to be a possible correlation which is worth investigation.

A further line of preventive treatment has been suggested in the endeavour to reduce the blood cholesterol, and it is hoped at the same time the incidence of coronary disease, by the oral administration of large doses of *nicotinic acid:* up to 900 mg. a day. Such a total daily intake, even if split up into divided doses, provokes marked vasodilatation in many subjects and has therefore disadvantages, but it is found that a number of patients acquire tolerance to these side-effects and can take the drug with relatively little discomfort.

The third line along which prophylaxis of recurrent myocardial infarction is practised is by the *long-term use of anticoagulants*. For a number of years anticoagulants have been widely used in the treatment of acute episodes of myocardial infarction and, although there is still sharp division of opinion regarding the benefits to be expected from their use, there is general acceptance of this as a reasonable therapeutic measure. During the last few years it has been suggested that anticoagulant therapy might well be maintained indefinitely in individuals who are found liable to recurrent myocardial infarction, and I have used this form of treatment for some years in such patients as have suffered two myocardial infarctions in succession and in younger men, in their thirties and forties, presenting with a first infarct. Statistical proof of the value of such treatment has hitherto been lacking, but during the last two years a controlled trial sponsored by the Medical Research Council has been conducted on this problem. The published results suggest that there are sound grounds for the administration of anticoagulants on a long-term basis as a preventive measure, at least in the younger age-groups and particularly in men. The control of dosage must be in the light of blood tests for prothrombin activity, and clinical laboratories up and down the country are equipped to carry out this work. It is fortunate that experiments have shown that the test can be carried out on blood up to twenty-four hours old without loss of accuracy, which implies that blood can be sent to the laboratory through the post by doctors living at some distance. It is, of course, important that the patient's general condition should be reviewed at regular intervals, either by the doctor in person or at a clinic.

Finally in this question of the prophylaxis of coronary disease there is considerable evidence that the proportions of lipid in the blood transported as alpha- and beta-lipoprotein, conveniently estimated by electrophoresis, are modified by the *sex hormones*, and it may be that the relative immunity of young women to coronary disease is related to this fact. Attempts have been made to reduce the liability to coronary disease in men by giving them female sex hormones of the œstrogen group. By such treatment the lipoprotein pattern in the blood can be considerably modified,

but the side-effects of the treatment are such that the average man prefers to take his chance of a coronary relapse rather than submit to the therapy. The search goes on for some substance which will modify the blood lipoproteins without the sex-hormone effects which are manifest with the current preparations.

TREATMENT OF HEART FAILURE

The most significant advance in the last few years in the treatment of heart failure has undoubtedly been the introduction of oral non-mercurial diuretic drugs. One of the first of these was aminometradine, which, because of its gastro-intestinal irritant action, has now been replaced by amisometradine. The latter, in a dose of 400 mg. four times on one day and twice daily thereafter, produces a diuresis approximately equivalent to half that induced by a standard 2-ml. dose of intramuscular mersalyl. Probably the most popular and widely used of these oral diuretics is chlorothiazide, now supplemented by hydrochlorothiazide with a similar action and some ten times the potency of the parent drug. Other drugs of this group include hydroflumethiazide, which differs from chlorothiazide in containing fluorine and a saturated thiadiazine ring. The dose is comparable to that of hydrochlorothiazide.

Such compounds are now being used extensively in the treatment of patients with cardiac failure as a substitute for injected mercurial diuretics, with obvious advantages in ease of administration and acceptability by the patient. Chlorothiazide is a potent diuretic and has been found extremely valuable in the management of the ambulant cardiac patient who has been in failure. Drugs of the chlorothiazide group, however, promote a marked increase in potassium excretion with a striking effect on the digitalis therapy which is commonly used simultaneously. It is recognized that a low blood potassium enhances digitalis action; in fact, in patients who, for one reason or another, have received an overdosage of digitalis, the administration of potassium salts is a recognized method of treatment. In my experience cases of mild or moderate digitalis overdosage are much commoner today than they were a few years ago, both among patients referred to hospital for admission and among patients actually under treatment in my wards. The cause would appear to be this potentiation of digitalis action by the potassium-losing effects of chlorothiazide. It is important therefore that the practitioner who is administering digitalis and chlorothiazide to any patient should periodically review the dosage of digitalis critically in the light of possible toxic effects. Where estimations of blood potassium are feasible, these should be done from time to time. A wise general measure is to give such patients a potassium supplement by mouth: say, potassium chloride 0.5 g. a day. It should further be remembered that chlorothiazide has a well-established action in potentiating the action of ganglion-blocking drugs, so that when using chlorothiazide the dose of mecamylamine (pentolinium) or pempidine may have to be halved. The dose of chlorothiazide is

0.5 g. twice daily, which should be given only for two or three days at a time in each week. When hydrochlorothiazide is used the dose is one-tenth of this: namely 50 mg. twice daily.

DRUG TREATMENT OF HYPERTENSION

In the drug treatment of hypertension the search continues for a ganglion-blocking agent with a selective action on the sympathetic as opposed to the parasympathetic nervous system. Recently, a new type of compound with the promise of great advantages has been tested in certain clinics. This is bretylium tosylate—a drug with a selective action on the sympathetic nerve endings—with which it is claimed that parasympathetic side-effects are minimal or absent. All the ganglion-blocking agents so far in general use (hexamethonium compounds, pentolinium, mecamylamine and the latest addition, pempidine) share the disadvantage that reduction of pressure tends to be accompanied by undesirable side-effects referable to paralysis of the parasympathetic, either in the eye (accommodation) or the alimentary tract (dryness of the mouth and constipation of varying intensity). Pempidine is claimed to have advantages over the older members of this group in that the stabilization of the patient on an appropriate dose is more readily achieved and the spacing of dosage is convenient. A usual initial dose is 2.5 mg. four times a day, increased by 2.5 mg. daily until a satisfactory reduction in blood pressure is achieved. In general, a daily dosage of 25 to 35 mg. a day is average. As with other compounds of this type the simultaneous administration of chlorothiazide will result in marked increase in potency and necessitate reduction in dosage of the ganglion-blocking drug; this, of course, is an advantage in avoiding side-effects. Similarly, the simultaneous administration of Rauwolfia compounds (reserpine) will achieve a reduction in dosage.

It cannot be too strongly emphasized that the key to success in the use of hypotensive drugs lies in close clinical supervision of the individual patient and adjustment of the dosage of the drug to the response achieved. Further, a decision to start such therapy is not to be reached lightly since a patient with a moderate degree of hypertension may not require treatment of this type and may, in fact, be harmed by it. Certainly treatment should be instituted in patients with malignant hypertension, with a very high diastolic pressure (140 mm. Hg or over), evidence of cardiovascular, renal or cerebral lesions, and marked changes in the retinæ. Treatment is also indicated in patients with high pressures of the order of 200/110 mm. Hg or thereby, particularly if there is evidence of incipient breakdown, especially in the cardiovascular system. It is unwise to attempt to treat moderate degrees of hypertension (say, 160/100 mm. Hg) in the absence of symptoms, and particularly in women around the menopause; such degrees of raised pressure may be sustained for many years with little or no disability and attempts to treat the blood pressure rather than the patient are ill advised. Finally it is wise for any individual doctor to confine himself to the use

of a single drug of the series since, by selecting one of these drugs and using it intensively in a series of patients, he will come to know the drug and the response to be expected, and will achieve better over-all results than one who chops and changes from drug to drug as new proprietary remedies appear. One need hardly reiterate that the casual prescription of these potent remedies without close supervision of the effect produced in the individual patient is tantamount to malpractice. Such can only lead to entirely inefficient management of the hypertension and at worst may lead to tragedy, either through unwarranted hypotensive effects or through severe complications, particularly intestinal ileus.

ANTI-LEUKÆMIC DRUGS

There is ample evidence that leukæmias of all types are today more common than they were twenty years ago, particularly the acute leukæmias of childhood and early life. This increased incidence of what is in effect a neoplastic disease of the bone marrow has obvious interest for the geneticist and for those concerned with the effects of radiation, whether from terrestrial or cosmic natural sources, or man-made. The practical implication is the avoidance so far as possible of exposure to radiation: e.g. the prohibition of x-ray apparatus in shoe-shops; avoidance of needlessly repeated barium meals in peptic ulcers; circumspection in referring orthopædic patients for repeat films and of lung and cardiac patients for screening.

For many years, x-ray therapy has been used in the treatment of chronic leukæmias with an action comparable to that of x-radiation in the treatment of malignant disease of conventional type. A number of drugs now used in treating leukæmia has a similar action to x-radiation in respect of arresting cell division, and detailed study of their mode of action has shown a striking similarity between their effects and that of x-rays. Drugs of this type are exemplified by busulphan, urethane, and the nitrogen mustards. A second group of drugs of great potency and entirely different action is in use: metabolic antagonists which appear to interfere with substances essential for cell division and growth. To this group belong certain derivatives of folic acid, aminopterin and amethopterin, and mercaptopurine. Urethane (dose usually 1 g. thrice daily) and busulphan (dose 1 to 4 mg. daily) are of most value in the treatment of chronic myeloid leukæmia, their action being comparable to that of x-ray therapy. In chronic lymphatic leukæmia x-ray therapy probably remains the most effective method of treatment. In the acute leukæmias the folic acid antagonists, aminopterin and amethopterin, are of some value but have extremely severe side-effects which may militate against their value in the treatment of this desperate disorder. These drugs are of similar action and have an equivalent effect, but the dose of amethopterin is about five times that of aminopterin: i.e. approximately 2.5 to 5 mg. a day. Side-effects (dermatitis, buccal ulceration, diarrhœa, and hæmorrhage from the gut) are common and indicate withdrawal of the drug. If tolerated, the drug should be continued till a remission

occurs or up to a maximum of six weeks. The side-effects are of such intensity, however, that these drugs must be used with extreme caution even in acute leukæmia. A less toxic drug, mercaptopurine, in a dose of 2.5 mg. per kilogram of body weight daily may induce a remission after three to four weeks' administration; the side-effects are less formidable and less frequent than with the folic acid antagonists.

Cortisone is a drug free from the unpleasant and dangerous side-effects of those previously mentioned, and is effective in a proportion of cases, although its action is unpredictable and it may fail to influence the course of the disease. About half the victims, however, may be expected to benefit from a course of one of the cortisone group. Dosage initially is high—200 to 300 mg. a day—and is later reduced to the lowest level which will maintain the patient in remission. Naturally, the side-effects and dangers of cortisone therapy in this condition are similar to those in other conditions for which the drug is used.

ORAL IRON PREPARATIONS

The use of oral iron preparations in the treatment of chronic microcytic, hypochromic, or iron-deficiency anæmia has long been standard practice, a variety of ferrous salts having been used. There is a tendency today to decry ferrous sulphate as irritant and to substitute more expensive preparations of the gluconate or succinate of iron as being less toxic. The results of a well-controlled trial using the modern double blind method with statistical control have recently been published in which no significant difference in toxicity or hæmatinic activity was found between the various iron preparations. It was found, for example, that unknown 'control' pills, thought by the subjects to contain iron but which in fact contained only lactose, produced as much nausea and intestinal upset as iron pills. There would thus appear to be no reason for the prescription of the more 'elegant' and expensive gluconate and succinate preparations in preference to ferrous sulphate in equivalent dosage.

ANÆMIA IN PREGNANCY

The investigation of anæmia in pregnancy has taken on added significance since it has been demonstrated in several parts of the country that the incidence of megaloblastic anæmia in pregnancy is much higher than had previously been supposed. This disorder can be detected by skilled blood examination, particularly if the hæmatologist examines either the bone marrow or, more simply and safely, the 'buffy coat'. The diagnosis is important since the disease is potentially dangerous and is resistant to iron, although it responds dramatically to folic acid the use of which in this condition appears to be free from any risk of promoting the development of neurological complications, such as occur when it is used in cases of Addisonian pernicious anæmia. One might emphasize here that folic acid, while fully active in restoring the blood picture and bone marrow to normal in per-

nicious anæmia, is known to accelerate, or even produce, the spinal cord changes of subacute combined degeneration. It is a drug which should *never* be used without a specific indication: e.g. pernicious anæmia of pregnancy, anæmia of malabsorption syndrome.

THE MALABSORPTION SYNDROME

During the last decade a remarkable advance has taken place in our knowledge of the etiology of this curious syndrome, commonly referred to as 'idiopathic steatorrhœa' or 'non-tropical sprue'. The clinical syndrome though uncommon is familiar, and is characterized by passage of an increased number of bulky malodorous stools containing a high proportion of fat, associated with some distension of the abdomen in an otherwise thin or emaciated subject and commonly associated also with tetany, rickets, anæmia, or a tendency to hæmorrhage. All these clinical features can be related to failure of absorption of various dietary factors: e.g. fat, iron, calcium, folic acid, vitamin K. During the last decade it has been demonstrated that the defect in absorption is not 'idiopathic' but is determined by intolerance to the gluten fraction of wheat flour. In the comparable disease in children (cœliac disease) the exclusion of gluten from the diet leads in a very high proportion of cases to complete clinical remission of the disorder. In adults the response is by no means so uniform and only about half the patients are significantly improved; moreover, in the adult improvement may be slow in onset. Nevertheless, the response may be significant if a sufficient time on the gluten-free diet is allowed for thorough test. Adjuvant therapy, by giving intramuscular iron and calcium and by administration of vitamins, particularly folic acid, vitamin D and vitamin K, may be necessary. It is important to realize that when a gluten-free diet has been consumed for some time a return to normal diet may provoke as a rebound a striking deterioration in the patient's condition. This is of particular importance in practice, since patients who have been well maintained on the régime in hospital may without the knowledge of the practitioner return to ordinary diet at home, with disastrous effects. It is possible today in most big towns to obtain gluten-free flour for baking purposes and in some to buy gluten-free bread.

HEPATIC COMA AND RELAPSING HEPATITIS

Hepatic coma.—The occurrence of coma in patients with severe liver disease has long been recognized. Recently it has been shown that it is often related to the absorption of toxic substances from the gut, particularly where a large portal-systemic shunt allows such substances, absorbed from the gut into the portal blood stream, to enter directly into the venous blood, which in turn reaches the brain. There is evidence that these substances may be derived from bacterial action on nitrogenous material and in such patients there is commonly a rise in blood ammonia. The recognition of the biochemical abnormalities in this disorder has led to a rational régime

of treatment, the principles being the withdrawal of dietary protein, the institution of purgation and the administration of oral chlortetracycline. Such measures are of value both in cases of hepatic pre-coma and of fully developed coma occurring either in the course of an acute episode of liver cell necrosis or following gastro-intestinal hæmorrhage in liver cirrhosis. In cases with chronic impairment of liver function modified forms of this régime may be of value, particularly the continued restriction of dietary protein and in some cases the long-term administration of an oral antibiotic: e.g. neomycin.

Relapsing hepatitis.—A second feature of liver disease of current interest is the demonstration that in a proportion of cases of relapsing hepatitis the continued progress of the disorder may be due, not to a prolonged viral infection but to a species of auto-immunization, comparable with that which is known to occur in some cases of thyroiditis. In some cases of this type it would appear that the body has become sensitized to its own liver cells, and that an antigen-antibody reaction occurs with continued destruction of the cells of this essential organ. Such being the case, it is logical to attempt to depress the antigen-antibody reaction by cortisone, and this substance has in fact been found of value in a proportion of cases of relapsing hepatitis. Untreated, the course of this disease is inexorable and a trial of cortisone in patients suffering from it is certainly justifiable.

HÆMOCHROMATOSIS

A third condition which is best considered as an alimentary disorder is hæmochromatosis, long familiar as 'bronze diabetes'. The fundamental defect here is in the absorption of iron from the gut, which is greatly in excess of that in the normal individual. As a result iron accumulates in the body, the serum iron level is uniformly high and the iron-binding capacity of the plasma proteins is practically saturated. The fibrosis of liver, pancreas and kidney which occurs in hæmochromatosis is a sequel to the deposition of iron. A comparable condition can be induced by repeated blood transfusions, which may lead to the deposition of iron in considerable quantities in the body stores. It is not possible to produce such a condition in normal individuals by oral administration of iron preparations, but a similar condition may be induced by overdosage with parenteral iron, whether by intramuscular or intravenous injection. The treatment of hæmochromatosis today is logically an attempt to deplete the body stores of iron by repeated venesections. On an average, 1 pint (570 ml.) is withdrawn each week over a period of two months or more. It is important that this treatment should be controlled by frequent estimations not only of the patient's hæmoglobin but of the total serum-iron and the saturation of the plasma proteins, or serum iron-binding capacity, since depletion of the body's iron stores leads to a fall in the serum iron and a rise in the unsaturated portion of the plasma proteins before anæmia actually develops. Once depletion of the body stores has been achieved, infrequent venesections may maintain the

patient in balance. This is an important advance in treatment, since hæmochromatosis is now recognized as being much commoner than had previously been suspected: twenty years ago it was looked upon rather as a medical curiosity.

CARCINOMA OF THE LUNG

In a survey of respiratory disease in Britain today several salient features emerge. In the first place there is the striking and progressive rise in the incidence of bronchial carcinoma, which now ranks high among the major causes of death, particularly in middle-aged and elderly males. There are also the widespread occurrence of, and severe disability which is caused by, chronic bronchitis and the present recession in the incidence of pulmonary tuberculosis.

As to the cause of the high and rising incidence of cancer of the lung there seems sound evidence on statistical grounds that this is associated with the modern widespread increase in cigarette smoking, and it would appear that there is *prima facie* sound reason for the campaigns now being waged up and down the country to discourage smoking, and in particular to discourage smoking among boys, for these days the 10- or 12-year-old who smokes his regular daily ration of cigarettes is a familiar feature alike in town and country.

In the treatment of bronchial carcinoma the crux of the matter is early diagnosis. Only too often the surgeon or radiologist is confronted with a patient who is already the victim of advanced disease, a patient in whom there is massive collapse of a lobe or of a lung, in whom there is a large blood-stained pleural effusion, in whom there may be secondarily involved lymph glands in neck or axillæ, a large carcinomatous liver, or secondary deposits in bone or brain. Such patients are in general beyond hope of rescue or even of palliation. On the other hand, when the carcinoma is diagnosed at an early stage, surgical excision is feasible and the results encouraging. It is important therefore that every doctor should be aware of the various ways in which bronchial carcinoma may present, so that it may be diagnosed at a stage long before the blatant physical signs of the inoperable case become all too obvious. Hæmoptysis is a common symptom and the type of hæmoptysis may be of diagnostic value. In other conditions (tuberculosis, pulmonary infarction, mitral stenosis) hæmoptysis may be brisk in amount but is seldom persistent over a period of more than a day or two. In cases of bronchial carcinoma, on the other hand, the blood may be scanty in amount but it may continue to be coughed up over a period of many days or weeks. Such hæmoptysis should always arouse suspicion of a possible underlying carcinoma. Again, cases of ill-defined pneumonia in middle-aged men, responding it may be reasonably well to a course of penicillin or other antibiotic, but in whom there are persistent signs (crepitations, poor air entry) or in whom x-ray examination reveals a failure of complete resolution within a week or two, are commonly associated with

an underlying bronchial carcinoma. Such cases should therefore be investigated fully with this possibility in view at an early stage of their illness. The essence of success in early diagnosis in this condition as in so many others is twofold: first that the doctor should be aware of the possibility of the existence of a carcinoma, and secondly that he should take the trouble to look for it.

CHRONIC BRONCHITIS

Today chronic bronchitis is no longer looked upon with the same benevolent tolerance as was customary a decade ago, when it was commonly regarded as more of a nuisance than a real disability. It was not then realized how many individuals are handicapped over a period of years by recurrent attacks of winter cough, leading eventually to gross impairment of respiratory function and to cardiac failure. The etiology of bronchitis is still uncertain but there is mounting evidence that atmospheric pollution plays a not insignificant role. This is particularly well seen when 'smog' envelops a major city, with a striking increase in the death rate from respiratory disease in that area during that time. It would appear that certain constituents of the polluted air are particularly potent in provoking the bronchitic reaction; prominent among these is sulphurous acid, formed in the water-laden atmosphere from sulphur dioxide, which occurs in industrial smoke from many sources. There is considerable evidence also that diesel fumes may play a part and, of course, there is no question that cigarette smoking is an important prejudicial factor.

Some points in the management of chronic bronchitis are worthy of attention. First of these is the treatment of the individual suffering from an acute intercurrent respiratory infection, going on maybe to capillary bronchitis or broncho-pneumonia, in whom respiratory function is already impaired and in whom the superadded burden of the acute infection proves a grave hazard. In such patients the anoxia consequent upon the capillary bronchitis produces not only cyanosis of the extremities but a brisk rise in the pulmonary blood pressure which in turn increases the load on an already overburdened right heart, with the result that right heart failure commonly supervenes. This condition of cor pulmonale associated with swelling of the ankles, enlargement of the liver, engorged neck veins and deep cyanosis is familiar today and is, in general, of grave import. The logical treatment is by the administration of penicillin or other appropriate antibiotic to control the infection and by the administration of oxygen to relieve the anoxia. With this twofold attack on the underlying cause of the right heart failure, generally speaking the myocardium picks up reasonably well. Digitalis and its allies are disappointing as cardiotonic drugs in handling such cases. Reference should be made to the fact that some patients in this condition, blue from anoxia but conscious, may on breathing oxygen in high concentration rapidly become pink and comatose. This curious therapeutic paradox is due to the fact that in these individuals the poisoned

respiratory centre is no longer sensitive to carbon dioxide fluctuations but is responding to anoxia. When the anoxia is relieved the breathing stops and carbon dioxide accumulates to an even higher level in the blood stream causing hypercapnia and coma. This serious complication of oxygen therapy can easily be avoided; either by giving oxygen intermittently for ten or fifteen minutes every hour, or by giving oxygen at first in rather lower concentrations than would otherwise appear desirable.

The treatment of the chronic bronchitic between episodes of respiratory infection demands passing notice. The action of antibiotics on the established infection is so striking that it is tempting to attempt to suppress such infections by long-term oral antibiotic administration. Certainly by giving such preparations, the number and severity of bronchitic relapses can be strikingly reduced. There are disadvantages, however: on the one hand, the side-effects of oral antibiotic therapy (fungus infection of the mouth and the alimentary tract, diarrhœa); on the other, particularly with chloramphenicol, the possibility of provoking bone-marrow depression with aplastic anæmia. Nevertheless, the risks of repeated severe acute infections to such patients are such that it is justifiable to attempt to suppress infections by such therapy.

As regards symptomatic treatment in bronchitis there is general agreement today that the old-fashioned expectorant cough mixture has outlived its usefulness and very little use is made of potassium iodide, ammonium carbonate, ipecacuanha and squills in modern prescribing. Attempts to liquefy the sputum have been made, using inhalations of minute dry particles of enzyme constitution. These can be inhaled from nebulizers of a type in general use today for the intrapulmonary administration of other substances—bronchodilators such as isoprenaline and drugs of the cortisone group. Such inhalers are charged with finely divided powdered drug which is delivered in a measured dose in the form of a cloud and inhaled by the patient deep into the recesses of his respiratory tree. With small particles it can be shown that access to the alveoli is gained, and there is a striking increase in the efficiency of such medication as compared with normal parenteral or oral administration of the drug. In the bronchospasm of asthma, for instance, it is possible to give isoprenaline repeatedly in doses so small that effects on pulse rate and blood pressure are negligible while the effects on the bronchial musculature are marked. Such insufflators would appear a valuable ancillary tool in the handling of chronic bronchitis and the asthma with which it is so often associated.

TRACHEOTOMY

A major innovation in the treatment of respiratory disease during the last few years has been the recognition that tracheotomy holds a place in the treatment of respiratory infections and of severe status asthmaticus. The operation is indicated in patients in whom bronchospasm is of extreme severity and persistence so that cyanosis is deep and consciousness clouded

or lost, and in patients in whom gross exudate into the bronchi is occurring which the patient is unable to expel by coughing, either through general physical weakness or through impairment of the elasticity of the chest as in emphysema. The rationale of the operation is threefold. By tracheotomy it is possible to reduce the dead space in the respiratory tract by 100 or 150 millilitres. Secondly, the resistance to respiration which exists at the level of the larynx and pharynx is short circuited. Thirdly, through a tracheotomy opening it is possible to aspirate secretions repeatedly and efficiently from the trachea without disturbance of the patient, certainly with much less upset than through the intact larynx.

An example of this was under my care during the influenza epidemic in the spring of this year—a woman in whom repeated bronchoscopic aspiration of tracheal and bronchial secretion afforded only temporary relief and in whom tracheotomy appeared to play a life-saving role.

A similar life-saving effect was demonstrable in a recent patient with severe status asthmaticus admitted in a deeply cyanosed and unconscious state, who had failed to respond to the ordinary treatment applicable for that condition.

When the patient's unaided respiratory efforts are inefficient it is possible to supplement these with positive pressure respiration from an appropriate pump.

This was used effectively in one patient who some years before had suffered from a severe form of poliomyelitis requiring treatment in an iron lung. The residual muscular paralysis was such that in the course of the pneumonia, for which he came under my care, his unaided respirations were entirely inefficient.

TUBERCULOSIS

Today the general incidence of tuberculosis in the population is falling with one notable exception—that amongst elderly men. In this sex and age-group the incidence is rising, and the detection and treatment of such cases constitute a major problem. Happily the post-war wave of tuberculosis which led to such difficulty in accommodating in hospital all those requiring treatment has largely subsided, and with the advent of efficient chemotherapeutic measures the domiciliary treatment of many erstwhile hospital-type cases has become feasible. It is interesting to note that up and down the country hospitals built and staffed originally for the treatment of pulmonary tuberculosis are now either being closed or are being diverted to other purposes.

CEREBRAL VASCULAR DISEASE

It is now recognized that a proportion of cases of hemiplegia are due, not to vascular obstruction or hæmorrhage in the classical lenticulo-striate and lenticulo-optic arteries, but to occlusion of the internal carotid artery or common carotid trunk on one side. The diagnosis may be suspected clinically from palpation of the common carotid artery, a diminished pulsation on one side being noted in cases in which the common carotid trunk is affected, but proof of the diagnosis is afforded by arteriograms. The recognition that obstruction of such vessels can occur raises major therapeutic problems. For example, there is a possibility that the early use of efficient

anticoagulant therapy in a patient developing the syndrome might forestall complete occlusion and avert disaster. On the other hand, with modern techniques, including hypothermia which permits the cutting off of blood supply to the brain for ten minutes at a stretch without damage, it is possible for repair or grafting of the affected vessel to be carried out by a surgeon skilled in such specialized work. The syndrome is mentioned here simply to remind practitioners that cases of hemiplegia should not casually be dismissed as due to intracerebral hæmorrhage or thrombosis without at least considering the possibility that an accessible artery may be the seat of occlusion and therapy may be possible. Unfortunately, the hopes once entertained that vasodilatation might be achieved by stellate ganglion block have not been realized.

Another type of cerebral vascular accident in which surgery holds out the hope of cure is of course subarachnoid hæmorrhage, and all patients up to the age of 50 or thereby developing such a hæmorrhage should be referred as soon as possible to a neurosurgical clinic for assessment and possible operation. The mortality during the first few weeks from recurrent hæmorrhage is so high that all possible steps should be taken at an early stage to have feasible cases dealt with surgically.

WILSON'S DISEASE

One other disease of the central nervous system, hitherto baffling, has recently been explained. This is Wilson's disease, in which progressive destruction of the basal ganglia is associated with liver cirrhosis. For long the etiology remained obscure, but work in the last decade has shown that we are dealing with a fundamental upset of copper metabolism. The traces of copper normally ingested from the gut with the diet are bound to a specific protein in the blood stream and as such are removed from the possibility of harmful effects. When the particular protein responsible for the binding and carrying of copper, cærulo-plasmin, is deficient, the copper is attached loosely to other proteins in the blood and is deposited with great facility particularly in two sites: the liver and the basal ganglia. In each of these this poisonous metallic ion sets up a hostile reaction and liver cirrhosis and basal ganglion disease result. The demonstration of the mechanism, which is genetically determined, is of great interest from a theoretical point of view but it carries a therapeutic implication. It is not possible to reduce the ingestion of copper from an ordinary diet to negligible proportions, but it has been found that penicillamine has the property of promoting copper excretion and by its continued administration it is possible, as it were, to purge the body of copper in much the same way as repeated venesections will purge the body of iron in the comparable condition of hæmochromatosis. This treatment, highly expensive and highly specialized, is not yet in general use but it is already being carried out in this country.

ADVANCES IN SURGERY

By JOHN BRUCE, C.B.E., P.R.C.S.Ed., F.A.C.S.
Regius Professor of Surgery, University of Edinburgh

Surgical progress—philosophical as well as practical—is generally the result of two distinct operations. In the first place, from the perimeters of contemporary thought or practice a salient is thrust forwards, usually in consequence of new 'intelligence' acquired in the sciences ancillary to surgery. The new position may prove to be untenable, or it may need to be adjusted; but, if a new vantage point is sustained in advance of the previous frontier, the second phase ensues—the phase of consolidation, of integration, and eventually of further exploitation.

In the last year there has been no spectacular leap ahead on the surgical front, but there has been a continuous process of consolidation in respect of positions already achieved. Indeed, throughout the whole field of surgical endeavour, there have been important and steady developments in all aspects of surgical care. During the past few years surgeons have become increasingly interested in the failures of surgery, and the pathological and physiological setting in which they occur. In consequence, it is now possible to predict with remarkable accuracy the hazards of injury, disease and operation in the light of the individual patient's personal biological and pathological status; and the emphasis in current therapeutic philosophy is on the individual and not on his disease. It is for this reason that there are few surgical patients for whom some form of helpful, if not necessarily ideal, treatment cannot be designed. It is, in fact, increasingly possible to 'tailor' our therapy to a patient's needs rather than submit his disease to a standard form of management. This is now generally recognized by our colleagues in other disciplines, and by our patients, so that today surgical stock stands at its highest.

One other important trend of recent years has continued: that of the integration of surgery and its allied and ancillary sciences, both in research and treatment. Exciting new discoveries are the fruits of team work, and some of the complicated operations of today—as on the open heart—and some of the operations in complex disorders—as in hæmophilia—and the management of such lethal complications as acute respiratory insufficiency and acute renal failure are only possible by a team, of which the surgical member is sometimes not the most important. This is a development not yet reflected in hospital construction or organization, but in years to come its implementation will exercise the ingenuity of both clinicians and planners.

SURGICAL SHOCK

The steady increase in the number of accidents, and at all ages, continues to highlight the gaps in our knowledge of traumatic or surgical shock, but

there have been some advances in our concepts of the fundamental morbid physiology as well as in our therapeutic management.

Since the last war, emphasis has rightly been placed upon loss of circulating blood volume as the main cause of the peripheral circulatory failure in shock; and restoration of the circulating volume is the most important object of our therapy. It is generally appreciated, however, that some patients fail to respond to energetic volume replacement even by blood; and some of the causes of this are now known. Prominent among them are inadequate transfusion through under-assessment of the degree of blood loss, the presence of severe muscle damage, and massive infection at the site of injury.

Hypoxia.—Less well recognized is the adverse influence of hypoxia, which may be a consequence of blood loss but, that apart, is particularly important in injuries to the chest wall, such as multiple rib fractures with 'paradoxical' respiration, and in injuries to the lung itself. Even without associated blood loss, the hypoxic patient is hypotensive and cyanosed, and the peripheral circulation is gravely reduced. When, in addition, much blood has been lost—as in multiple injuries—the condition is a grave one and even adequate blood replacement effects little if any improvement, death occurring from acute and massive pulmonary œdema. Acute hypoxia may also contribute to postoperative shock when there is interference with pulmonary ventilation, or reduction in the gas exchange surfaces as a result of chronic bronchitis and emphysema, or when there has been pre-existing anæmia with consequent shortage of hæmoglobin for the transport of oxygen. The submission of elderly patients to extensive operations has of late years emphasized this hazard, and encouraged measures for its prevention and treatment.

Acute hypoxia takes precedence in the management of the shocked patient. Oxygen and the provision of a clear airway by posture or by intubation, the stabilization of a paradoxically moving chest wall by operation or sternal traction, the restoration of controlled thoracic wall mobility by relieving the pain of fractured ribs by strapping or local anæsthesia, and repeated bronchoscopic aspiration of secretions are the most important measures.

Tracheostomy.—In the elderly, in whom the pulmonary ventilating surface is often reduced, and in the unconscious, in whom the natural elimination of bronchial secretions is impossible, the insertion of a temporary tracheostomy tube (tracheostomy) may be preferable to very frequent bronchoscopy, and indeed may be life-saving. A tracheostomy is now often established to prevent chest complications in elderly patients with respiratory disease undergoing elective surgery; it reduces the respiratory dead space by by-passing the column of air in the upper respiratory passage, and it provides an easy and effective means for the administration of a high concentration of oxygen—if needs be by positive pressure respirator—and for the regular evacuation of secretions.

Carbon dioxide retention.—Another less common but striking respiratory syndrome may be encountered after chest injury or pulmonary collapse, or after operations on the chest: the syndrome of carbon dioxide retention. Here, despite efficient oxygenation, lung ventilation is insufficient to reduce the alveolar concentration of carbon dioxide. Since oxygen saturation of the arterial blood is adequate, the patient is warm, the skin flushed or suffused, sweating is profuse, and mental confusion gradually merges into coma. The blood pressure is normal, or even raised, and diagnosis is safely made on the clinical picture of sweating and flush in a patient who is normotensive. Retained carbon dioxide may be removed by closed-circuit respiration with a CO_2 absorber, either through a cuffed intratracheal tube or a temporary tracheostomy.

DANGERS OF MASSIVE AND REPEATED TRANSFUSIONS

Large quantities of stored blood may be called for in the treatment of acute renal failure by the artificial kidney, in shock, in gastro-intestinal hæmorrhage and in some forms of radical ablative surgery. In general, modern techniques of collection, preservation and transfusion are so competent that the risks of blood administration are few, although every now and then anuria results from a mismatched transfusion, and careful observation is necessary, especially in the elderly, to avoid circulatory overload. When blood replacement is massive or transfusion has to be repeated, as in recurrent gastro-intestinal hæmorrhage, two important but unusual complications may be encountered.

Citrate intoxication.—In the first place, the citrate in the stored blood removes the ionized calcium from the host serum, leading to impaired muscular activity and cardiac irregularity with electrocardiographic changes. This citrate intoxication can be prevented—and corrected—by the administration of a gramme of calcium gluconate along with every 3 to 4 pints of blood.

Hæmorrhagic tendency.—The second complication is the development of a dangerous hæmorrhagic tendency associated with gross reduction in blood platelets, increased fibrinolytic activity and reduction in the anti-hæmophilic globulin of the serum. Blood coagulation is a highly complicated process and the elucidation of errors in it is a highly skilled laboratory exercise. Since the exact cause of the bleeding tendency after repeated transfusions is not clear, treatment is empirical, and, in the main, consists of transfusions of fresh blood and the administration of calcium gluconate. More specific therapy—the use of fibrinogen, lyophilized fresh frozen plasma (antihæmophilic factor) and corticosteroids (for the thrombocytopenia) should be guided by expert hæmatological opinion. The clinician does well if he recognizes the disorder, and the surgeon especially if he recalls the possibility of it in 'closed' injuries when other causes of irreversible 'shock' have been excluded, since it may cause hidden continued bleeding into body cavities and tissue planes.

ELECTIVE OPERATIONS IN HÆMOPHILIAC PATIENTS

The 'spontaneous' hæmorrhagic lesions of hæmophilia occasion so much anxiety and disappointment that, rightly, operations for unassociated conditions are to be avoided whenever possible. Nevertheless, the work of Macfarlane, Biggs and their co-workers at Oxford has enabled their surgical colleagues to intervene successfully, not only in trauma where operation may be imperative, but in conditions, such as duodenal ulcer and tuberculosis of the kidney, where operation is desirable. The sheet anchor in clinical management is the replacement of the patient's deficient serum antihæmophilic globulin (A.H.G.) with globulin derived either from active human blood or from animals. The foreign A.H.G. has a short life, and the insurance of an effective level during and after operation calls for repeated assay which is the special responsibility of the hæmatologist. Nevertheless, the surgical obligations are very significant: they consist of an operation as atraumatic as possible and so unhurried that there is time to secure all obvious bleeding points, however small; and the insurance of rapid healing by careful repair techniques and the avoidance of wound sepsis. A number of major elective operations have now been successfully undertaken in this country.

ACUTE RENAL FAILURE

There has been considerable progress in the management of acute renal failure due to pathological lesions in the kidney that are not irreversible. In surgical practice these may complicate extra-renal obstructive lesions of the urinary tract, or be a sequel to shock or burns with prolonged hypotension and anoxia, to operations in jaundiced or in toxic patients, or to mismatched blood transfusion. The changes in the kidney consist of acute necrosis of the tubular epithelium (acute tubular necrosis) and, while this runs its course, renal function is abolished and renal secretion ceases. If the patient can be sustained for a sufficient time, however, the tubular epithelium regenerates, and urinary flow is re-established.

It seems possible that mild degrees of tubular necrosis with minor oliguria may not be rare after major surgery, and are probably repaired without therapeutic intervention. Continued suppression is a serious complication, however, and the development of an effective 'artificial kidney' that permits dialysis of the blood and consequent adjustment of the electrolyte content is an advance of the first magnitude. Many recover without recourse to dialysis, of course: restriction of fluid intake to the amount necessary for inevitable losses by skin and respiration (about 500 ml.) and a high-calorie diet of glucose and fat will tide most surgical non-obstructive anurias over the critical period. If the patient's condition continues to deteriorate, and the blood urea rises to 400 mg. per cent., and especially when potassium retention reaches a dangerous level (7 mEq. per litre), the patient should be put on the artificial kidney. The potassium level falls in thirty to forty-five minutes, and at the end of a six-hour run

the chemical composition of the serum can be restored approximately to normal. Like most other advances, the care of the anuric demands the services of a team of doctors, nurses, biochemists and hæmatologists; at present, these resources exist only at special centres to which patients have to be transferred. It is obviously good policy to alert the centre before the clinical situation becomes critical and to effect transfer before the patient is moribund, even if eventually the use of the artificial kidney is unnecessary.

THE 'ARTIFICIAL KIDNEY' IN LIVER FAILURE

The ability of the artificial kidney to clear the blood of retained nitrogenous substances in anuria has prompted its use in liver failure with hepatic coma associated with an increase in the blood ammonium content. When the liver is grossly diseased the method has been unsuccessful, but in the acute coma that may follow massive gastro-intestinal bleeding from œsophageal varices dialysis may restore consciousness and lower the blood ammonium by as much as 50 per cent.

ANTIBIOTICS IN SURGERY

The expectation that prophylactic antibiotic treatment would prevent wound sepsis and infective postoperative chest complications has not been fulfilled; and the increase in the number of resistant strains of staphylococci in the hospital environment, contributed to by the indiscriminate use of penicillin, has created what is perhaps the major problem confronting the surgeon today. Intensive research is being directed to the problems of '*hospital infections*'; at the moment it seems likely that modifications in theatre design and ventilation, in methods of sterilization and other matters of theatre technique may be called for; and that some ward practices hallowed by nursing tradition will have to go by the board. The major hospital infections are staphylococcal. The infection is by no means confined to the main wound; sepsis at the site of an intravenous infusion, and postoperative staphylococcal chest lesions may both give rise to septicæmia and death.

At present the indications for prophylactic antibiotic therapy are few: as a preparation for large bowel surgery (though even here some surgeons have modified their former practice), in large wounds of the soft tissues, particularly when there has been muscle damage, and whenever large raw surfaces are created, as in burns. In the treatment of established infections, neglect of surgical principles and protracted inadequate administration of an antibiotic may mask a low-grade inflammatory lesion and greatly prolong ill health. This is important in abdominal surgery, since unequivocal signs of subphrenic or pelvic inflammation may be long delayed. It sometimes happens that in low-grade infected lesions the pathological response is non-suppurative, but in the form of a mass of vascular granulation tissue which is sometimes so prolific that a 'tumour' is formed. The differentiation of these 'antibiomas' from cancer may be difficult, especially in the breast and in the right iliac fossa.

PROGRESS IN REGIONAL SURGERY

There have been few striking advances in regional surgery, but both opinion and practice have become crystallized in respect of many of the new developments of recent years. Thus, the surgery of congenital heart defects is now established on a sound clinical basis, as regards both selection and method. It appears that most cardiac operations can be safely undertaken with the patient rendered hypothermic; only the repair of defects in the intraventricular septum demands the use of one of the methods of cardio-pulmonary by-pass. Although by no means the last word on the subject, it is gratifying to British surgeons that the pump-oxygenator designed by Melrose and his co-workers at Hammersmith has come to be regarded as the best and simplest yet produced.

The development of a serum agglutination test for chronic thyroiditis (Hashimoto's disease and Riedl's struma) has aided in the differential diagnosis of thyroid cancer, and spared many patients an unnecessary operation. Furthermore, close study of this group of diseases has inspired a new concept—auto-immunity—in the etiology of disease generally that may well have important applications elsewhere than in the thyroid gland.

In abdominal surgery there have been certain advances in our diagnostic resources. In the past, peptic ulcers situated beyond the duodenal bulb were usually missed, as the lesion was hidden by a normally filled duodenal cap. As a consequence, many with genuine and severe symptoms were condemned as neurotics. The lesion, however, can be demonstrated by a competent radiologist who screens in the lateral and oblique positions, or who uses stereoscopic views. The possibility of a lesion distal to the cap should always be considered when symptoms are atypical. The post-bulbar ulcer may present first as chronic or as massive acute bleeding, or as an obstructive lesion associated with much vomiting or as an ulcer-type dyspepsia with a large 'back-pain' component. In such circumstances a negative radiological report following conventional radiology is worthless and special examination of the post-bulbar region should be insisted upon.

The development of an oral water contrast medium (oral 'urografin', 'gastrografin') has extended the usefulness of radiology in the diagnosis of certain acute upper abdominal emergencies. The patient is given 40 to 60 ml. of the contrast medium, and screened; a 'no touch' technique which avoids abdominal palpation with its attendant dangers. The method has been used with success to determine the source of gastro-intestinal bleeding in the acute stage. Apart from the value of accurate diagnosis at this time, the substance has the added advantage over barium sulphate in that in patients who require operation the colon is not loaded with barium at laparotomy. 'Gastrografin' has been used postoperatively to detect leaks from suture lines and also in the diagnosis of perforated peptic ulcers; and delineation of the outline of the stomach and duodenal curve after its administration has also enabled the diagnosis of acute and subacute pancreatitis to be reached with some certainty.

PEPTIC ULCERATION

The exact etiology of peptic ulceration is unknown, and we still have to fall back on the old 'equation' of pathogenesis: acid secretion versus mucosal resistance. Fortunately, these provide a logical and successful target for surgical treatment, and in the last few years there has been substantial progress in the surgical approach to the disease. The routine use of the 'maximal histamine test', which provides an accurate measure of the gastric secretion when the stomach is subjected to a maximum stimulus, has enabled us to compare one patient's gastric secretory activity with another, and to place a 'quantitative' value on our surgical objective.

Gastric ulcer is not associated with gastric hypersecretion, but is accompanied by mucosal degenerative changes loosely called gastritis. The ulcer is confined to the area of 'sick mucosa', and the object of operation is to remove the vulnerable parts—the lesser curve and the antrum.

Duodenal ulcer, on the other hand, is almost invariably associated with gastric hypersecretion. Whether this is a response to overactivity of the normal stimuli or the result of an excessive amount of acid-producing tissue, it can be satisfactorily controlled in most instances both by excision of acid-bearing tissue (gastrectomy) or by eliminating the acid-evoking stimuli (vagotomy and antrectomy). Secretion studies of the acid production by the gastric remnant after standard gastrectomy have shown that the most that is accomplished by the operation is a reduction of secretion by 70 per cent. of the preoperative level. In a small group (7 to 10 per cent.) of duodenal ulcer subjects, however, the preoperative secretion is so gross that this degree of reduction is insufficient to guarantee against the development of postoperative stomal ulcer: in these patients a very high gastrectomy combined with vagotomy—or a gastrectomy, modified to remove all, or a larger part, of the fundus—is mandatory.

The majority of duodenal-ulcer subjects are moderate hypersecretors and, in these, standard gastrectomy sufficiently reduces the gastric secretion. A similar reduction, however, is achieved both by vagotomy and gastroenterostomy, and by vagotomy and antral excision. At first sight therefore it seems a matter of individual preference which procedure is selected, although it must be conceded that the more conservative operations carry virtually no mortality, and have fewer late sequelæ with the one exception of diarrhœa. If the recent suggestion that the diarrhœa is due to denervation of the cœliac plexus and that this can be avoided by leaving the appropriate division of the posterior vagus nerve is substantiated, it may be hard to justify the continued use of gastrectomy in the average case.

At the moment, surgical opinion already seems to be veering towards vagotomy and gastroenterostomy, but unquestionably the most important current development is the quantitative estimation of the patient's needs before submitting him to any form of surgery and the selection of a method which is certain to achieve the primary objective of operation, i.e. the permanent cure of the peptic ulcer disease. In the elective surgery of duodenal ulcer, the day of the 'blind' gastrectomy is mercifully over.

ADVANCES IN OBSTETRICS AND GYNÆCOLOGY

By NORMAN MORRIS, M.D., F.R.C.O.G.

Professor of Obstetrics and Gynæcology, Charing Cross Hospital Medical School

WHEN I was younger and less cynical an article entitled 'advances' always attracted my interest. Time has taught me that most of these articles, particularly those related to obstetrics and gynæcology, only confirm the previous suspicion that there have really been few positive advances. The obstetric world, just like the world outside, thirsts for 'advances'. Since there has been so little real progress there is a tendency to over-enthuse about very modest and often rather dubious achievements. The medical press is certainly not short of articles but how few of these contain anything that is truly original. The majority restate all that has gone before and sometimes mere change of fashion is hailed as progress. It is an exhausting process sifting through the mounting mass of medical literature in an attempt to find the few articles which describe work of real merit and which make a contribution to the advance of knowledge.

This present article will confirm once again that there have been very few advances of any significance. Recent correspondence in the national press has drawn attention to the general dearth of clinical research in this country. This is particularly true for obstetrics and gynæcology. There are still so few centres where any really progressive research programme is in operation. One reason is that obstetricians in training are encouraged to spend several years taking their F.R.C.S. rather than devoting this period to completing a worth-while research project. A different system operates on the Continent and much more original work is produced.

The topics which I have selected for consideration are those which have attracted most interest in recent years.

PREPARATION FOR LABOUR

Grantly Dick Read died a few months ago. During his lifetime his theories and teaching provoked considerable controversy, but then of course he was a vivid and provocative personality. He lived long enough, however, to see a great deal of his teaching adopted and even the Cranbrook Report (1959) urges an increased development of the preparation classes for labour which he originally started. Read was certainly one of the first to draw attention to the all-important emotional aspects of pregnancy and labour. Even today in many centres these emotional factors receive too little attention. Pregnancy and labour are still regarded as purely physical and mechanistic events. Many of our antenatal clinics and labour wards can hardly be regarded as humane places. Development in this sphere is still

very slow and often the facilities provided in hospital reflect all the worst features of an institutional existence, surrounding labour with a morbidity, drabness and apprehension.

During recent years there has been increasing interest throughout Europe in another form of psychological preparation for labour. This is usually referred to as the 'psychoprophylactic method'. The books of Lamaze (1958) and Chertok (1959) give full descriptions of this method and although it does have a great deal in common with that of Read yet there are several important differences. The classes which the woman attends include a full description of the anatomy and physiology of pregnancy and labour. Many psychological reactions are also considered. This method was originally evolved in Russia and it is claimed that it is based on Pavlovian physiology. A detailed description is therefore given of the development of conditioned reflexes and also of some aspects of the physiology of sensation in general and of pain in particular. It is also claimed that by the energetic practice of relaxation and breathing exercises during labour a new series of conditioned reflexes can be built up which successfully inhibit the appreciation of pain by the cerebral cortex. Analgesics are rarely given, since it is considered that these impair cerebral activity and disturb the woman's ability to sustain her concentration. It is therefore a rather more active and intense method than that of Read. So far as I know there is no centre in this country which has as yet adopted this technique.

Between six and eight lectures are usually given by a doctor. In addition there is a similar number of physiotherapy classes. This system therefore does make considerable extra demands upon the medical staff and some critics claim that the results are not commensurate with the extra work involved. What is too often forgotten, however, is that any programme of health education and prophylaxis tends to be an expensive departure, at least in its early stages. I have visited various centres in Belgium, France and Austria where this method has been adopted and it is my impression that it is relatively more successful than the Read system. There is still a reasonable number of patients in whom it fails and we need to know more about the long-term effect upon these women, who are inevitably made very conscious of their own inadequacy. In time it should be possible to single out these prospective failures and thereby provide for them an alternative method based perhaps entirely upon analgesia.

RADIATION IN OBSTETRICS

During recent years there has been an increased realization that excessive radiation for medical purposes can possibly lead to harmful results. Although radiation may obviously have very serious long-term effects, the immediate one seems to be the likelihood of developing leukæmia. Alice Stewart and her colleagues at Oxford (1956, 1958) have produced evidence that suggests that acute leukæmia in children is related to x-ray examination of the mother's pelvis and abdomen during pregnancy. For this reason it has now

become common practice to limit any initial x-ray examination of the mother's pelvis to a single lateral film. If this initial film shows evidence of a contracted pelvis then further films may be taken. Since this new policy was introduced obstetricians are tending to find that they can often get along without x-ray examinations, and depend more and more upon careful clinical assessment. The question of leukæmia following irradiation has recently been reviewed by Burnet (1958), who drew attention to the new peak in the age distribution of between 3 and 4 years. He does not conclude, however, that the whole of the increase in leukæmia is attributable to irradiation of the mother: in fact, he suggests that if there are one hundred cases of leukæmia in childhood, eighty-four have no experience of irradiation in fœtal life. Of the sixteen who have received radiation a little more than half can be subtracted as being destined to suffer from leukæmia without radiation, so that only 7 per cent. of childhood leukæmia can be ascribed to irradiation of the fœtus *in utero*.

Other reasons must therefore be sought to explain the definite increase in the incidence of leukæmia. Burnet suggests that we should look for something connected with changes in social habit or with obstetric and neonatal care during and since 1940. Some possibilities are cigarette smoking in women, changes in the drugs commonly used in pregnancy, such as those used to control morning sickness, or in the induction of anæsthesia, or possibly changes in artificial feeding methods. Other possibilities include the effects of eating foods from which naturally occurring radioactive substances are concentrated.

ANTE-PARTUM HÆMORRHAGE

Of all present-day obstetric emergencies probably the most serious is *accidental hæmorrhage*. It is still impossible to single out those women in whom accidental hæmorrhage is likely to occur, even though it is still relatively more common in women with hypertension. The associated shock and afibrinogenæmia, together with the later development of oligural and anuria, still cause a considerable number of deaths. In many instances these deaths are due to a failure to recognize the condition in its eariy stages, followed by a failure to institute adequate transfusion in good time. Whilst over-transfusion must always be avoided, yet in these cases adequate and rapid transfusion can often be an all-vital life-saving measure.

The exact explanation for the development of *afibrinogenæmia* is still to be found, but the most commonly accepted theory is that a thromboplastin is liberated from either the decidua, placenta or amniotic fluid into the general circulation and that thereby an extensive deposition of fibrin takes place. This complication responds dramatically, of course, to the intravenous administration of fibrinogen.

TOXÆMIA OF PREGNANCY

The exact explanation of toxæmia of pregnancy still remains unknown. Our knowledge of the pathology and physiological changes, however, is

becoming more complete. Browne (1958) advanced the theory that it is due to the inability of the placenta to counteract the over-activity of the adrenal cortex, which normally occurs during pregnancy. This inability to counteract the influence of the adrenal cortex, he suggests, arises from the development of placental ischæmia which in turn is consequent upon the failure of the body to adapt itself to the pregnancy syndrome. Before this theory is finally accepted a great deal more work is required to fill in the present gaps in our knowledge.

Probably the most interesting work during the past year was that published by MacGillivray and Buchanan (1958). Using $NaCl^{24}$ and KCl^{42}, they studied the total exchangeable sodium and potassium in normal and pre-eclamptic patients. Their studies showed that the total exchangeable sodium is increased in normal pregnancy and in pre-eclampsia. There is also a slight increase in the total exchangeable potassium in both normal and pre-eclamptic pregnancy. The most interesting finding was that the amount of sodium retained in pre-eclampsia is the same as in normal pregnancy, but there is greater retention of water in pre-eclampsia than in normal pregnancy. It is therefore concluded that sodium retention is not the cause of œdema in pre-eclampsia and that this œdema is probably due to the effect of the anti-diuretic hormone. Hawkins *et al.* (1958) have also published interesting details of their estimations of the electrolytes in uterine muscle in normal and pre-eclamptic pregnancy. These show a definite disturbance of the intracellular sodium/potassium ratio in regard to pre-eclampsia. The exact significance of salt in the development of the pre-eclamptic syndrome is therefore still uncertain, but meanwhile it is still customary to limit the intake of sodium in pregnancy. Robinson (1958), however, has published results of her work, which are based on giving women extra salt during pregnancy and she claims that this actually reduces the incidence of, and helps to cure, pre-eclampsia.

ESSENTIAL HYPERTENSION

A recent symposium (1958) studied extensively the significance of non-toxæmic hypertension in pregnancy. Many interesting observations emerged and it was quite clear that the prognosis in pregnancy of the women with a raised blood pressure, even of a modest degree, is not so satisfactory as that of the normotensive patient. Nevertheless, there are women with even gross degrees of hypertension who may go through several pregnancies and produce living infants, without an apparent deterioration in their hypertension. The great difficulty in this problem of 'essential' hypertension is to select those women who are going to deteriorate from those who will have a straightforward time. At present there is also no reliable method of assessing the efficiency of placental function, which is one of the most important factors involved. Bechgaard (1958) showed that the ultimate prognosis of women who have hypertension following pregnancy toxæmia is far worse than those who have hypertension before the pregnancy begins.

A particularly interesting study has been described by Dixon and Robertson (1958), who have taken biopsies of the placental bed in normotensive and hypertensive women. These biopsies confirm that there are extensive vascular changes in the placental bed in women who suffer either from hypertension or from toxæmia of late pregnancy. They claim that similar changes are not to be found in normal patients.

PLACENTAL INSUFFICIENCY

It is becoming more apparent that the majority of stillbirths are related to failure of the placenta to meet the requirements of the fœtus *in utero*. There is still much we do not know regarding the changes in placental metabolism during both the early and the middle stages of pregnancy, but in particular in the later months. In many instances the placental insufficiency is associated with such established disorders as toxæmia, essential hypertension and diabetes mellitus. In other cases the mother appears perfectly normal and there is no clinical evidence of any abnormality of the pregnancy; when the baby dies the death is entirely unexpected. This kind of case in particular may happen from the 28th week onwards and accounts for a large percentage of the so-called unexplained stillbirths, which do occur at this time.

Scott Russell and his colleagues (1957) have developed a technique of assessing placental function by estimating the pregnanediol in the urine. As it is necessary to perform serial estimations of the pregnanediol in the urine, this method is only applicable to cases in which some degree of placental insufficiency is already present. Since we have no other scientific means of assessing placental function this work is a valuable step forward.

UTERINE CONTRACTILITY

There has been considerable study of the action of the uterus in recent years. The work of Alvarez and Caldeyro-Barcia (1950, 1952) is of particular interest in this direction and has led to a greater appreciation of the various forms of uterine activity that may occur during labour.

A new synthetic oxytocin has been introduced ('syntocinon') and this has been shown to be free from hypertensive effect. Injection of oxytocin ('pitocin') and 'syntocinon' drips are being widely used both in the induction of labour and also in the stimulation of the uterus after the membranes have been ruptured surgically. Undoubtedly the use of such a drip does enable far more women to go into labour after the membranes have been ruptured, although failures still occur and occasionally Cæsarean section is still necessary. For this reason induction of labour can still not be undertaken lightly and we have yet to find an efficient and safe way of inducing labour.

HEART DISEASE IN PREGNANCY

There has been increasing public interest in cardiac surgery, due to the publicity that has been given to the operations involving 'a hole in the heart', and there have been several recent articles discussing the value of

cardiac surgery in pregnancy (Das and Chesterman, 1958; Winter *et al.*, 1958; Watt *et al.*, 1959). These indicate that in certain cases of coarctation of the aorta and mitral stenosis, surgery can be safely and profitably undertaken. Before a woman is allowed to continue with her pregnancy, however, with the idea in mind that she may have surgery performed, it is most important to ensure that the case under consideration is suitable for surgical treatment.

MANAGEMENT OF LABOUR

Pethidine is still the main analgesic being used in present-day practice. Its effect is enhanced by the simultaneous administration of chlorpromazine. Alternatively some obstetricians are now using 200 mg. of pethidine as their standard dosage. The risk of inducing asphyxia in the baby is much less since there are antidotes, such as nalorphine, which can be administered intravenously to the mother just before the baby is born.

Heyns (1959) has published an exciting article on the use of a decompression suit during labour. This consists of a fibre-glass case, which surrounds the abdomen and in which the pressure is reduced. By this means the uterus becomes more spherical. He publishes results which suggest that this has two effects: (i) the length of labour is reduced by half; (ii) the pain appreciated by the patient is also considerably diminished. This preliminary publication is most encouraging and, if later results confirm the initial impression, this new approach may prove to be a very great advance indeed.

STAPHYLOCOCCAL INFECTION IN HOSPITAL

A large number of maternity hospitals all over the country have been closed during the past two years by outbreaks of disturbing staphylococcal infections in the newborn. These have often been of the Phage Type 80 and the reason for concern is that most of the staphylococci involved have been resistant to penicillin. Several studies have now been published of the effect of such epidemics. (Wysham *et al.*, 1957; Gillespie *et al.*, 1958; Timbury *et al.*, 1958). These reports confirm the great difficulties that arise in hospital in preventing the cross-infection of babies. The umbilical cord in particular is a common site for the transfer of infection even though it may show no obvious clinical abnormality. Maternity units of the future will undoubtedly have to pay more attention to this important problem of cross-infection. More isolation facilities will have to be available. We have recently discovered in one of our units that many women coming into hospital already have a staphylococcus in their throat or nose, which is penicillin resistant. This suggests that it is not always the hospital which is responsible for the development and transfer of these organisms to the mother or baby. Barber (1956) has described very clearly the method whereby staphylococci appear to become resistant to antibiotics.

VAGINAL CYTOLOGY

The vaginal smear is now used extensively throughout most university

centres in Europe and America for the early detection of carcinoma of the cervix or uterine body. In many cities general practitioners perform routine screening of their patients and send in the smears they obtain for examination at the hospital centre. In this country there has been little enthusiasm for this method and relatively few centres exist. This is probably to be regretted, since, although this screening method is inevitably rather costly, nevertheless it does often enable cancer to be diagnosed at a stage when there is every hope of a reasonable cure. So many of the cases of carcinoma we see in hospital practice are too far advanced for any treatment to be effective. This method of early diagnosis also uncovers quite a large number of cases of carcinoma *in situ*. It is known that some of these patients do recover spontaneously and that the change observed does not always advance to a frank carcinoma. Unfortunately, there is considerable difficulty in sorting out those that will go on to carcinoma and those that will not, and it is therefore necessary to screen these women repeatedly and very carefully if they are young and still wish to have children. At a later age a total hysterectomy is usually performed, even though some of these cases are also known to be capable of spontaneous regression.

CARCINOMA OF THE CERVIX AND UTERUS

In most centres the usual initial treatment of carcinoma of the cervix is radium therapy. This is sometimes followed by a Wertheim's hysterectomy, but in general some additional form of radiotherapy is usually preferred. Some centres in this country are now using the linear accelerator for this purpose. It has the advantage of causing less pigmentation and irritation of the skin and it is also claimed that a much more even dosage can be distributed to the whole pelvis. Treatment of carcinoma of the body of the uterus has become rather varied in recent times. Preoperative radium therapy is sometimes given, followed by total or Wertheim's hysterectomy. In other places surgery is followed by radiation therapy, either in the form of deep x-rays or by the application of a radium plaque to the vault of the vagina. The advantages of these various techniques are still not finally established. One cannot help feeling that if it were necessary to register precisely all cases of cancer, with an exact description of the treatment that is given, we should then be able to reach a much more rapid conclusion as to the best form of treatment.

VAGINITIS

During recent years there has been increasing interest in non-specific vaginitis (Heltai and Taleghany, 1959). The exact etiology of this condition is not yet understood and there is still considerable argument as to whether the *Hæmophilus vaginalis* is the organism of importance. Even if it is, various other organisms are usually found to be present as well. For this reason the condition often responds to administration of lactic acid in the form of pessaries, together with triple sulphonamide vaginal pessaries or creams.

Monilial vaginitis can now be treated much more readily by the use of nystatin (Jennison and Llywelyn-Jones, 1957) and this form of treatment is obviously a great step forward over the more old-fashioned method of gentian violet.

CONCLUSION

Space does not allow consideration of several other interesting topics. I make no apology for having given more attention to obstetrics, since in my view this seems a unique specialty with many particular and hopeful fields for investigation. Some of these investigations may well relate to many problems in general medicine. Gynæcology, on the other hand, apart from the problems of endocrinology and infertility, is really a subdivision of general surgery. Until there is a major general break through in the treatment of cancer, 'advances' in gynæcology will continue to revolve around descriptions of interesting pathology, minor changes in operative technique and the seemingly unending argument regarding the value of surgery, radiation or both.

References

Alvarez, H., and Caldeyro-Barcia, R. (1950): *Surg. Gynec. Obstet.*, **91,** 1.

Barber, M. (1956): In 'Lectures on the Scientific Basis of Medicine', 1956-57, London, vol. 6, p. 333.

Bechgaard, P. (1958): In 'Symposium on Non-Toxæmic Hypertension in Pregnancy', London, p. 192.

Browne, F. J. (1958): *Lancet*, **i,** 115.

Burnet, M. (1958): *New Engl. J. Med.*, **259,** 423.

Caldeyro-Barcia, R., and Alvarez, H. (1952): *J. Obstet. Gynæc. Brit. Emp.*, **59,** 646.

Chertok, L. (1959): 'Psychosomatic Methods in Painless Childbirth', London.

Das, J. B., and Chesterman, J. T. (1958): *Brit. med. J.*, **i,** 142.

Dixon, H. G., and Robertson, W. B. (1958): *J. Obstet. Gynæc. Brit. Emp.*, **65,** 5, 803.

Gillespie, W. A., Simpson, K., and Tozer, R. C. (1958): *Lancet*, **ii,** 1075.

Hawkins, D. F., Nixon, W. C. W., and Whyley, G. A. (1958): *J. Obstet. Gynæc. Brit. Emp.*, **65,** 6, 911.

Heltai, A., and Taleghany, P. (1959): *Amer. J. Obstet. Gynec.*, **77,** 11, 144.

Heyns, O. S. (1959): *J. Obstet. Gynæc. Brit. Emp.*, **66,** 2, 220.

Jennison, R. F., and Llywelyn-Jones, J. D. (1957): *Brit. med. J.*, **i,** 145.

Lamaze, F. (1958): 'Painless Childbirth', London.

MacGillivray, I., and Buchanan, T. J. (1958): *Lancet*, **ii,** 1090.

Report of the Maternity Services Committee (1959): H.M. Stationery Office, London.

Robinson, M. (1958): *Lancet*, **i,** 178.

Russell, C. S., Paine, C. G., Coyle, M. G., and Dewhurst, C. J. (1957): *J. Obstet. Gynæc. Brit. Emp.*, **64,** 5, 649.

Stewart, A., Webb, J., Giles, D., and Hewitt, D. (1956): *Lancet*, **ii,** 447.

——, ——, and Hewitt, D. (1958): *Brit. med. J.*, **i,** 1495.

Symposium on Non-Toxæmic Hypertension in Pregnancy (1958): London.

Timbury, M. C., Wilson, T. S., and Hutchison, J. G. P. (1958): *Lancet*, **ii,** 1081.

Watt, C. L., Bigelow, W. G., and Greenwood, W. F. (1959): *Amer. J. Obstet. Gynec.*, **77,** 3, 507.

Winter, W. R., Carmichael, D. B., Baronofsky, I. D., and Baker, W. S. (1958): *Ibid.*, **76,** 3, 572.

Wysham, D. N., Mulhern, M. E., Navarre, G. S., LaVeck, G. G., Kennan, A. L., and Giedt, W. R. (1957): *New Engl. J. Med.*, **257,** 295.

ADVANCES IN PÆDIATRICS

By DOUGLAS HUBBLE, M.D., F.R.C.P.
Professor of Pædiatrics and Child Health, University of Birmingham

THE advances in pædiatrics continue on a broad front. The pædiatrician, electing to occupy himself with a narrow sector of medicine, finds that a great number of specialists both in and outside medicine are increasingly interested in pædiatric problems to the great advantage of his science and craft. In the following article most attention is given to the etiology and recognition of new syndromes and the modern treatment and prevention of long-known diseases. The last paragraph on chromosomes contains a reference to the most exciting discovery of the pædiatric year: the discovery that mongols have an extra chromosome. Will it be the most significant?

MENTAL DEFICIENCY AND INBORN ERRORS OF METABOLISM

The list of congenital enzymatic defects associated with mental deficiency grows steadily longer. To the now well-recognized disorders—phenylketonuria, galactosæmia, Wilson's disease, goitrous cretinism, Hartnup disease and sucrosuria—have recently been added two other examples. Allen and his colleagues (1955) described a familial mental disorder associated with a disturbance of amino-acid metabolism. Both the urine and the cerebrospinal fluid contain large amounts of an abnormal peptide, which is, however, in low concentration in the plasma. As a possible explanation of this unusual finding it is suggested that the peptide is formed in the brain and rapidly excreted by the kidneys.

In the second disorder, the plasma, cerebrospinal fluid and saliva have high concentrations of the three aliphatic amino-acids: valine, leucine and isoleucine. In the urine large amounts of the same amino-acids can be demonstrated by chromatography, together with their normal metabolites, the corresponding keto acids (Westall, Dancis and Miller, 1957; Smith and Strang, 1958; Mackenzie and Woolf, 1959; Dancis *et al.*, 1959). In addition, the urine contains large amounts of abnormal metabolites—the corresponding hydroxy acids—and Mackenzie and Woolf (1959) suggested that the keto acids are reduced by an abnormal pathway due to the absence of the enzyme carboxylase. The hydroxy acids give the urine a characteristic smell of maple syrup or burnt sugar, which was observed in the first cases described by Menkes, Hurst and Craig (1954). The name 'maple syrup urine disease' has therefore been used; if this characteristic smell in the urine is missed the disorder may be confused with phenylketonuria, for, although the chromatographic urinary patterns are quite separate, both the clinical condition and the ferric chloride reaction in the urine are not dissimilar. Although these patients may be expected to improve with a diet low in valine, leucine and isoleucine, such a diet is not practicable. Galactosæmia

can be permanently prevented by the elimination of lactose from the diet with virtual cure of the condition, and occasional reports are now appearing from several places of the value of dietary treatment (restriction of both phenylalanine and tryptophan to 25 mg. per kg. of body weight daily) in phenylketonuria. Brimblecombe, Stoneman and Maliphant (1959) report the case of a child, now aged $3\frac{1}{2}$ years, with normal intelligence in whom treatment was started at the age of 17 weeks. Diagnosis must also be made early in life, and in Birmingham the ferric chloride test for phenylketonuria is now being done on the baby's napkins in infant welfare centres. It is hoped that two or three new cases will thus be discovered each year. A genetic disorder no longer carries an irreversible prognosis.

INFANTILE SPASMS

Increasing interest has been taken recently in the condition of 'infantile spasms'. The children appear to develop normally in the first few weeks or months of life, then convulsions occur with jerky movements of the head or arms, and sometimes a very sudden single movement in flexion of the entire body ('salaam attacks'). Mental deterioration is rapid and the prognosis is poor. Gibbs and Gibbs (1952) pointed out a close correlation between infantile spasms and a characteristic type of electroencephalographic pattern which they called 'hypsarrhythmia'. Illingworth (1955) described the case histories of 12 children suffering from the condition. Bower and Jeavons (1959a) give an account of 22 patients with infantile spasms; in about half the cases there was a history of prenatal or perinatal cerebral damage. There is as yet no certain clue as to the etiology of this rare condition in those children who are in good health up to the age of six months or so.

Reports of treatment by corticotrophin (5 to 10 units of the gel daily for 10 to 15 days) have recently appeared (Sorel and Dusaucy-Bauloye, 1958; Low, 1958; and Stamps *et al.*, 1958) which show promise. Bower and Jeavons (1959b) have treated seven patients with corticotrophin for a period of one month, starting treatment for a further month if the patient relapses. They recommend a daily dose of at least 20 units for children of all ages. The electroencephalographic records have quickly become normal, the convulsions have disappeared and, if the treatment is applied early in the course of the disease, mental deterioration may be checked. It is imperative therefore that any baby developing infantile spasms should be referred immediately to an appropriate hospital for investigation and treatment.

NEONATAL COLD INJURY

Mann (1955) drew attention to the syndrome in infants which is associated with accidental exposure to cold. The diagnosis may well be missed if the rectal temperature—this is nearly always below 90°F. (32.2°C.)—is not taken, and a low-reading thermometer (range 85 to 110°F.) is required. In hospital the infant's condition is too readily attributed to an underlying infection, or, if hardening of the panniculus is observed, the clinician may be satisfied with the diagnosis of sclerema. The history is of increasing apathy

and anorexia, and the important physical signs are a reddening of the face and extremities associated with a mortuary coldness of the skin. There is usually œdema of the hands and feet, which always precedes the onset of sclerema. Despite these symptoms and signs the infant may not appear to be seriously ill. Investigations may reveal hypoglycæmia with acidosis (carbon-dioxide retention due to a depressed respiratory excursion) and various abnormalities are seen in the electrocardiogram. The complications in a severe case are infection and hæmorrhage into the skin, the gastro-intestinal tract and the lungs. Death supervened in eight out of Mann's 14 cases. In Birmingham, 70 cases of hypothermia due to neonatal cold injury have been observed in the last 11 years and of these 18 have died (Bower, Jones and Weeks, 1959). The treatment is by slow rewarming (in a room temperature of 70 to 80° F. [21 to 27.5° C.]), liberal glucose administration by intragastric drip, and antibiotic cover. Prevention depends on watchfulness to prevent a fall in room temperature which occurs so easily in this country in the winter, and certain infants may sustain damage in room temperatures as high as 55° F. (12.8° C.).

NEONATAL HYPERBILIRUBINÆMIA

Hyperbilirubinæmia in the infant may be associated with the deposition of bilirubin in the nerve cells of the basal ganglia—kernicterus—with resulting permanent brain damage. Lathe and his colleagues (Lathe and Ruthven, 1954; Lathe and Walker, 1957; Lathe, Claireaux and Norman, 1958) have shown that this depends upon a specific defect of hepatic function in the new-born child. This hepatic immaturity has now been shown to be related to an enzymatic defect: a deficiency of the enzyme glucuronyl transferase. Bilirubin is fat-soluble but before it can be excreted by the liver into bile or excreted in the urine it must be converted into a water-soluble form by conjugation with glucuronic acid and, in the absence of transferase, this indirectly-reacting pigment (van den Bergh reaction) circulates in the plasma and damages the nerve cells. The immature liver has an efficiency in the excretion of bilirubin which is only 1 to 2 per cent. compared with the adult, and it cannot deal even with the normal 1 per cent. of daily red-cell breakdown. Hence, when there is increased hæmolysis, as in hæmolytic disease of the newborn and congenital hæmolytic anæmia, or when there is any depression of liver function as in hypothyroidism or hepatitis, dangerous and prolonged hyperbilirubinæmia may result.

Exchange transfusion remains the only efficient therapy; exposure of the baby to sunlight and to a pale blue light have been disappointing treatments (Lathe *et al.*, 1958; Cremer *et al.*, 1958). The administration of sodium glucuronate (Danoff *et al.*, 1958), in an attempt to conjugate bilirubin, has not proved an effective method of therapy.

Three questions have emerged which are keenly debated and for which there are widely different answers. What is the critical level of bilirubin which may result in brain damage? What is the incidence of kernicterus

among premature babies? How often is exchange transfusion required in premature babies? One reason for the varied opinions concerning the critical levels of serum bilirubin exists in the varying liability of individuals to nuclear jaundice (Crosse, Meyer and Gerrard, 1955; Dine, 1954; Hsia *et al.*, 1952). Moderate opinion may be summarized in the statement that kernicterus is rare when the serum bilirubin is no higher than 15 mg. per 100 ml., that it may happen with levels between 15 and 30 mg. per 100 ml., and that it is nearly certain to occur when the level of bilirubin exceeds 30 mg. per 100 ml.

TUBERCULOSIS

The situation in respect of tuberculous infection in childhood becomes increasingly satisfactory. The deaths from tuberculosis in children under 15 years of age were 131 in 1957 as compared with 1,955 in 1947. A further index of progress in the control of tuberculosis is the reduction in the number of positive tuberculin reactions. In 1950, these were positive in 15 per cent. of children at the age of 5 years in the Medical Research Council investigation and the figure is now no more than 2 per cent. (Miller, 1958). Control of the disease depends upon case finding, the care of contacts, the supervision of tuberculin-positive children, and BCG vaccination.

BCG vaccination.—BCG vaccination in this country is now recommended for all tuberculin-negative children in contact with a person suffering from tuberculosis, for tuberculin-negative school-leavers aged 13-14 years, and for those whose work exposes them to special hazard, such as nurses and medical students. The M.R.C. inquiries (Medical Research Council, 1952, 1956) showed conclusively that both BCG and vole vaccination were effective in preventing tuberculosis. The vole vaccination has been discarded because of the delayed local reactions (axillary adenitis) which it produces.

Treatment.—The treatment of tuberculosis is by drugs, by *para*-aminosalicylic acid (300 mg. per kg. per 24 hours in divided doses), by streptomycin sulphate or chloride (10 to 20 mg. per kg. per 24 hours) and by isoniazid (5 to 20 mg. per kg. per 24 hours). Chemotherapy should be used as early in the infection as possible; it is now common practice to treat the child with the primary complex. Two drugs should be used together because this diminishes the risk of drug resistance developing. Recently, however, isoniazid has been used alone in the treatment of primary tuberculosis (United States Public Health Service Tuberculosis Prophylaxis Trial, 1957) and drug resistance does not appear to be causing trouble. In all severe infections, however, such as miliary tuberculosis, tuberculous meningitis and bone and joint tuberculosis, not less than two drugs should be employed together. The patients with a primary complex should be treated for a period up to one year, and those with severe infections for not less than two years.

NEPHROSIS

Etiology.—The etiology of nephrosis in childhood is still obscure but cases have been described as occurring after the use of drugs such as mercury

(Wilson, Thomson and Holzel, 1952), trimethadione and paramethadione (Barnett, Forman and Lawson, 1952; Wren and Nutt, 1953). It occurs in lupus erythematosus (Zetterström and Berglund, 1956) and in bilateral renal-vein thrombosis. It has occurred in siblings in 14 families (Vernier, Brunson and Good, 1957), and there is a fatal form of the disease which has been described in the newborn, particularly in premature babies (Giles *et al.*, 1957).

As to the primary pathological lesion, there is increasing agreement that this is an alteration in the basement membrane of the glomerular capillaries (Allen, 1955). Renal biopsy material studied with the electron microscope (Farquhar, Vernier and Good, 1957) has demonstrated this lesion together with a change in the epithelial component of the glomerular tuft, though whether the epithelial lesion is primary or secondary is arguable. The proteinuria is caused by an abnormal leakage of serum proteins from the glomerulus (Hardwicke and Squire, 1955), and this is confirmed by the similarity of urine and serum-protein constituents (Squire, Blainey and Hardwicke, 1957). There is tubular reabsorption of protein, although the extent of this reabsorption is debatable (Macaulay and McCrory, 1957). The glomerular capillary is envisaged as a membrane with a series of pores (Pappenheimer, 1953) which are increased in size in nephrosis; and the clearance rates of the various proteins vary inversely with the molecular size of the protein: the smaller the molecule, the greater the leakage. The albumin fraction has a molecular weight of 70,000 whilst the globulin fractions are not homogeneous, varying from 45,000 to 1,300,000 in molecular weight, yet the average molecular size of the protein components of globulin greatly exceeds that of the albumin fraction. The albumin clearance therefore always exceeds that of the globulin fractions. The hypoproteinæmia is thought to be accounted for by the proteinuria (Blainey, 1954), and the hyperlipæmia is a consequence of the inadequate metabolism of protein—a mobilization hyperlipæmia.

Treatment.—Steroid therapy is producing a much improved recovery rate and is delaying relapse, although it is too early to say how effective the treatment is in assuring long-term survival. Treatment should be begun early, and should be continued intensively for a month. Some pædiatricians then prefer continuous maintenance therapy with small doses, others prefer intermittent therapy (say, three days in each week), and others give no further therapy unless a relapse occurs.

Prednisolone should be used for one month in the first instance in doses of 2.2 mg. per kg. per 24 hours, the usual precautions being observed; and potassium chloride should be given (1 g. daily), especially during the diuretic phase. Diuresis is nearly always achieved, but complete biochemical reversal does not always occur, a degree of proteinuria sometimes remaining. The likelihood of successful therapy is directly related to the severity of the disease: the more severe the disease, as judged by the glomerular filtration rate, the albumin leak (as assessed by the ratio of the clearance of albumin

to the clearance of creatinine) and the amount of urinary protein, the poorer the response to steroid therapy (McCrory and Macaulay, 1957; McCrory, Fleisher and Rapoport, 1957). Prophylactic antibiotic therapy (benzylpenicillin 200,000 units twice daily, or phenoxymethylpenicillin, 60 mg. twice daily) should be used continuously. High-protein diets should be used unless pathological nitrogen retention occurs (Blainey, 1954).

When protein catabolic agents such as the steroids are used in long-term treatment, it is particularly important that continuing attention should be paid both to height increments and to bone structure. The child's height should be measured at each attendance, and a radiograph of the spine should be taken every six months. A dose of 50 to 75 mg. of cortisone daily (10 to 15 mg. of prednisolone) in older children is usually not sufficient to interfere seriously with the deposition of protein; in children under the age of 5 years, 25 to 50 mg. of cortisone daily can usually be given without ill-effect. If osteoporosis and growth failure are occurring, and if a reduction of steroid dosage causes a relapse, then the use of protein anabolizers, such as norethandrolone, is rational. Dexamethasone has been shown to cause a cumulative loss of nitrogen and calcium (Slater *et al.*, 1959), and it is not therefore the steroid of choice in the long-term treatment of children.

RHEUMATIC FEVER

Rheumatic fever is a disappearing disease but it still occurs sufficiently often to demand a general awareness of recent advances in treatment. When the diagnosis is established salicylates and cortisone (or an equivalent dose of prednisolone) should be used together as has been shown by Illingworth and his colleagues (Illingworth, 1958). The dose of salicylate used should be not less than 1 grain per pound (0.15 g. per kg.) per day of body weight and the dose of cortisone not less than 3 mg. per pound (6.6 mg. per kg.) per day. The treatment should be continued until the sedimentation rate has been normal for three successive weeks. Since the recommended doses of these drugs is high and toxic side-effects may be produced, these patients may be more safely cared for in hospital.

Since rheumatic fever is associated, both in the first attack and in relapse, with the beta-hæmolytic streptococcus, prophylactic penicillin therapy should be continued until adult life. Benzylpenicillin tablets 200,000 units twice daily (Committee of the Royal College of Physicians, 1957) or phenoxymethylpenicillin tablets, 120 mg. twice daily, should be used. The former preparation is a great deal cheaper than the latter and has been shown to be effective and should therefore be used.

LEUKÆMIA

Apart from the new knowledge of neonatal hyperbilirubinæmia already discussed, the most interesting, and perhaps hopeful, development in hæmatology has been in the etiology, prognosis and treatment of acute leukæmia. Alice Stewart (1959) has shown that, in a small minority of cases

(5 per cent.), x-ray examination of the mother in pregnancy may have had a precipitating influence on the development of the disease. There is also a possibility, having regard to the high proportion of x-rayed children who died of leukæmia between the ages of 2 and 4 years, that x-rays in infancy have hastened the onset of leukæmia in children already predisposed to it. The cytological differences between the various types of acute leukæmia in childhood have been shown by Wintrobe (1956) to have some prognostic importance. The granulocytic and monocytic types of leukæmia are resistant to therapy whilst those with the undifferentiated lymphoid cells usually respond well.

The treatment does not produce a cure, but remissions are obtained. Steroids produce an initial remission in nearly 100 per cent. (infants in the first year may fail to respond) and the cytotoxic agent, mercaptopurine, in about 50 per cent. of patients. Prednisone or prednisolone is used in a dose of not less than 1 mg./kg./day and mercaptopurine in the same dosage. There is no agreed programme of treatment; the remissions are not long. Most children die within eighteen months of the diagnosis of the disease.

CHROMOSOMES IN MAN

Many important subjects must be omitted from this short survey, such as the swift advances in endocrine and cardiac diseases, and in surgery of the œsophagus, the heart, the brain and the spinal cord. This article must not be concluded, however, without a reference to the fact that two new methods have been evolved which allow us not only to define chromosomal sex but, more recently, to count the chromosomes in human nuclei. The first is now a routine investigation in most laboratories: a buccal mucosal smear is examined and the chromatin-positive cells (female) counted. The chromatin is hyperchromatic, showing material in the nucleus which Murray Barr and his colleagues (Barr and Bertram, 1949) correctly forecast would represent the XX chromosomes. Ford (Ford and Hamerton, 1956) has developed a method of counting chromosomes in a cell suspension of bone-marrow nuclei. There are 46 chromosomes (not 48 as was formerly believed)—22 pairs of autosomes and one sex chromosome pair (XX—female, XY—male). The patients with the Klinefelter syndrome have been shown to have XXY sex chromosomes despite their male phenotype (Ford *et al.*, 1959) and the patients with the Turner syndrome have been shown to have XO sex chromosomes despite their (usually) female phenotype (Ford *et al.*, 1959). Even more interesting, and perhaps more significant for future advances in pædiatrics, is that the mongol has been proved to have an extra chromosome: 47 instead of 46 (Jacobs *et al.*, 1959). The additional chromosome is probably an autosome and the primary disorder probably lies in oögenesis.

References

Allen, A. C. (1955): *Amer. J. Med.*, **18**, 277.
Barnett, H. L., Forman, C. W., and Lawson, H. D. (1952): *Advanc. Pediat.*, **5**, 53.
Barr, M. L., and Bertram, E. G. (1949): *Nature (Lond.)*, **163**, 676

Billing, B. H., Cole, P. G., and Lathe, G. H. (1954): *Brit. med. J.*, **2**, 1263.
Blainey, J. D. (1954): *Clin. Sci.*, **13**, 567.
Bower, B. D., Jones, L. J., and Weeks, M. M. (1959): (In the press).
——, and Jeavons, P. M. (1959a): *Lancet*, **i**, 605.
——, —— (1959b): *Ibid.*, **i**, 1154.
Brimblecombe, F. S. W., *et al.* (1959): *Ibid.*, **i**, 609.
Cremer, R. J., Perryman, P. W., and Richards, D. H. (1958): *Ibid.*, **i**, 1094.
Crosse, V. Mary, *et al.* (1955): *Arch. Dis. Childh.*, **30**, 501.
——, Wallis, Patricia G., and Walsh, Anna M. (1958): *Ibid.*, **33**, 403.
Dancis, J., Levitz, M., Miller, S., and Westall, R. G. (1959): *Brit. med. J.*, **i**, 91.
Danoff, S., Grantz, C., Boyer, A., and Holt, L. E., Jnr. (1958): *Science*, **127**, 759.
Dine, M. S. (1954): *Amer. J. Dis. Child.*, **88**, 810.
Farquhar, M. G., Vernier, R. L., and Good, R. A. (1957): *Amer. J. Path.*, **33**, 791.
Ford, C. E., and Hamerton, J. L. (1956): *Nature* (*Lond.*), **178**, 1020.
——, *et al.* (1959): *Lancet*, **i**, 709.
Gibbs, F. A., and Gibbs, E. L. (1952): 'Atlas of Electroencephalography', 2nd ed., Vol. 2, Cambridge, Mass.
Giles, H. M., *et al.* (1957): *Arch. Dis. Childh.*, **32**, 167.
Hardwicke, J., and Squire, J. R. (1955): *Clin. Sci.*, **14**, 509.
Hsia, D. Y. Y., *et al.* (1952): *New Engl. J. Med.*, **247**, 668.
Illingworth, R. S. (1955): *Arch. Dis. Childh.*, **30**, 529.
—— (1958): In 'Recent Advances in Pædiatrics', edited by Douglas Gairdner, 2nd ed., London.
Jacobs, P. A., *et al.* (1959): *Lancet*, **i**, 710.
Lathe, G. H., *et al.* (1958): In 'Recent Advances in Pædiatrics', edited by Douglas Gairdner, 2nd ed., London.
——, and Ruthven, C. R. J. (1958): *J. clin. Path.*, **11**, 155.
——, and Walker, M. (1957): *Biochem. J.*, **67**, 9.
Low, N. L. (1958): *Pediatrics*, **22**, 1165.
Macaulay, D., and McCrory, W. W. (1957): In 'Proceedings of the Eighth Annual Conference on the Nephrotic Syndrome', New York.
McCrory, W. W., *et al.* (1957): *Amer. J. Dis. Child.*, **94**, 401.
——, and Macaulay, D. (1957): *Pediatrics*, **19**, 481, 639.
Mackenzie, D. Y., and Woolf, L. I. (1959): *Brit. med. J.*, **i**, 90.
Mann, T. P. (1955): *Lancet*, **i**, 613.
——, and Elliott, R. I. K. (1957): *Ibid.*, **i**, 229.
Medical Research Council (1952): *Ibid.*, **i**, 775.
—— (1956): *Brit. Med. J.*, **i**, 413.
Menkes, J. H., Hurst, P. L., and Craig, J. M. (1954): *Pediatrics*, **14**, 462.
Miller, F. J. W. (1958): In 'Recent Advances in Pædiatrics', edited by Douglas Gairdner, 2nd ed., London, p. 260.
Pappenheimer, J. R. (1953): *Physiol. Rev.*, **33**, 387.
Slater, J. D. H., *et al.* (1959): *Lancet*, **i**, 173.
Smith, A. J., and Strang, L. B. (1958): *Arch. Dis. Childh.*, **33**, 109.
Sorel, L., and Dusaucy-Bauloye, A. (1958): *Acta neurol. belg.*, **58**, 130.
Squire, J. R., Blainey, J. D., and Hardwicke, J. (1957): *Brit. med. Bull.*, **13**, 43.
Stamps, F. W., *et al.* (1958): 'Scientific Conference of the Brain Research Foundation'.
Stewart, A. (1959): *Lancet*, **i**, 1129.
United States Public Health Service Tuberculosis Prophylaxis Trial (1957): *Amer. Rev. Tuberc.*, **76**, 1942.
Vernier, R. L., Brunson, J., and Good, R. A. (1957): *Amer. J. Dis. Child.*, **93**, 469.
Westall, R. G., Dancis, J., and Miller, S. (1957): *Ibid.*, **94**, 571.
Wilson, V. K., Thomson, M. L., and Holzel, A. (1952): *Brit. med. J.*, **i**, 358.
Wintrobe, M. (1956): 'Clinical Hematology', 4th ed., Philadelphia.
Wren, J. C., and Nutt, R. L. (1953): *J. Amer. med. Ass.*, **153**, 918.
Zetterström, R., and Berglund, G. (1956): *Acta pædiat.* (*Uppsala*), **45**, 189.

ADVANCES IN THE TREATMENT OF SKIN DISEASES

By PETER BORRIE, M.D., M.R.C.P.

Physician, Skin Department, St. Bartholomew's Hospital

THE contemporary treatment of skin diseases falls naturally into two quite distinct categories. In the so-called constitutional maladies, where the pathogenesis remains obscure, therapy is entirely symptomatic, being directed towards controlling or suppressing the outward manifestations of the disease. Fortunately, many of these conditions are capable of complete and spontaneous resolution—a phenomenon which the uncritical may ascribe to treatment. The infectious diseases, on the other hand, are theoretically quickly and easily curable. The continually widening range of antibiotics and chemotherapeutic agents is bringing this goal into sight. Equally important, however, is the increasing knowledge of the epidemiology of these diseases, for in this way recurrent reinfection may be avoided. All these basic trends are well reflected in the following examples of recent advances in dermatological therapy.

ANTI-PRURITICS

Of all the symptoms which have to be treated as if they were the disease itself, itching is the most difficult to control. It is due to the liberation of certain proteolytic enzymes from epidermis, dermal infiltrates, micro-organisms or blood. These stimulate special non-myelinated, free nerve-endings in the epidermis or superficial dermis to send impulses to the brain via fibres which pursue the same course as pain fibres. The mechanism whereby certain locally applied substances decrease itching is not understood, except in the case of the local anæsthetics which obtain their anti-pruritic effect by paralysing the nerves. Drugs used systemically for the relief of itching are either sedatives or antihistamines. The latter only exert a specific action in urticarial eruptions; in all other itching conditions, what little effect they have is probably due to their central depressant effect.

The most recently introduced of these drugs, trimeprazine, although it does not represent any basic change in pharmacological approach, does, however, appear to have a greater effect (Anderson and Chalmers, 1959). It is a phenothiazine derivative lying pharmacologically between chlorpromazine and promethazine, and combines the central action of the former, without its anti-adrenaline effect, with the antihistaminic properties of the latter. It is also a powerful spasmolytic. The average dose is 10 mg. three or four times a day, but greater amounts have been given and the drug has been continued for a number of months. Although it can decrease itching in any cutaneous condition, its greatest effect seems to be exerted

in infantile eczema, Besniers' prurigo and neurodermatitis. It has also been used successfully in chickenpox. The commonest side-effect is drowsiness, although this may pass off after the first ten days of taking the drug. An occasional example of emotional disturbance and skin eruption has also been recorded. These are all well-recognized side-effects of phenothiazine derivatives in general and the other more severe effects, such as Parkinsonian symptoms, jaundice and blood dyscrasias, should therefore be watched for.

CORTICOSTEROIDS

Systemic.—Triamcinolone, a fluorine-containing derivative of hydrocortisone, has been used now for about two years and it is possible to make a fair assessment of its properties. It remains true that it is the only corticosteroid to have any consistent effect in psoriasis, improving or clearing the eruption in approximately 60 per cent. of cases (Shelley *et al.*, 1958). The malady returns, however, when the drug is discontinued and severe exacerbations have occurred following withdrawal, some of them being of the generalized pustular variety. On the other hand, in severe widespread or erythrodermic cases, especially when the degree of cutaneous inflammation precludes routine topical measures, triamcinolone can be invaluable. It should be reserved for these cases and should be used for as short a time as possible, bearing in mind the necessity of reducing the dose very slowly.

Its other use in dermatology is as a substitute for another corticosteroid already being employed. Apart from psoriasis, there are no conditions which habitually react more favourably to triamcinolone. On the other hand, in a severe dermatosis such as exfoliative dermatitis or pemphigus which is not responding satisfactorily to routine steroid therapy, triamcinolone should be tried and occasionally remarkable improvement is seen with equipotent doses. Since it causes less œdema and salt retention than other steroids, it is also particularly valuable in cases in which these side-effects are proving troublesome, or in cases with cardiac disease. In the absence of these indications, triamcinolone is actively contraindicated. It appears to cause hirsuties more quickly than other steroids, although this is usually reversible on stopping the drug. It also causes certain symptoms which appear to be peculiar to itself, notably post-prandial flushing, weight loss and muscular weakness. Finally, it causes a permanent dilation of cutaneous capillaries, leading to telangiectasia first on the face and later on the trunk and limbs.

Of the other recently introduced corticosteroids, methyl prednisolone has no particular advantages in dermatology. Dexamethasone, on the other hand, which like triamcinolone also contains a fluorine atom, may have some of the advantages of the latter without its disadvantages, but final judgment must be reserved until more clinical reports are available.

Topical.—Corticosteroids are used locally for two separate reasons: for their anti-inflammatory effect and for their anti-pruritic effect, and these

two properties appear to be distinct. To exert any effect at all they must be able to penetrate the epidermis to a certain extent and this penetration needs to be greater in order to produce a decrease of inflammation than of pruritus. Thus, the greatest anti-inflammatory action is obtained in areas where the epidermis is normally thin, for instance the eyelids, ears, face, neck and body folds; or in conditions which do not produce much thickening of the epidermis, such as acute and subacute eczematous eruptions. Where there is much lichenification, or where the horny layer of the epidermis is normally thick, the anti-inflammatory effect is weak. A decrease in irritation may still be produced under these conditions, however, and, due to less scratching, this can lead indirectly to improvement of the malady.

Having decided on whether the site and type of eruption are suitable for the use of topical steroids, it is next necessary to select the most effective vehicle for the drug. Here there are no hard and fast rules. On the whole the greasy ointment appears more effective than the non-greasy, with the lotion coming somewhere in between. Cases occur which respond dramatically to one base and not at all to another and a trial of more than one vehicle is sometimes worth while. These substances are also being marketed in the form of a spray. The results are no better, but it is arguable that the method may be cheaper if large numbers of patients are to be treated in hospital. Personally I have not found any use for this method of application and the obvious temptation to try it on the flies makes me hesitate to prescribe it for outpatients.

The third and final point to decide is the choice of corticosteroid. So far the only differences have been quantitative. Hydrocortisone is usually effective in a 1 per cent. strength or less, the 2.5 per cent. rarely being necessary. Prednisolone is equally efficacious in a strength of 0.25 per cent. (Inman, 1959). The advantage of this is purely financial, but none the less important. Triamcinolone in a strength of 0.1 per cent. is said to be even more effective (Smith *et al.*, 1958), particularly with regard to its anti-pruritic properties. It has, however, no effect on psoriasis and is considerably more expensive.

BACTERIAL INFECTIONS

The staphylococcus remains by far the commonest cause of skin infection. In a recent series of 212 cases of miscellaneous infectious conditions it was found in pure culture in 68 per cent. and was present in mixed culture in a further 24 per cent. (Lamont, 1959). The treatment of these maladies with local antibiotics must therefore be viewed against this background, bearing in mind that the criteria for choice of an antibiotic are three: the sensitivity of the organism, the potency of the antibiotic and its irritant effect on the skin. Of the bactericidal group, penicillin should not be used, not only because of the frequency with which it causes a reaction, but because of the increasing numbers of penicillin-resistant staphylococci. Streptomycin should also never be used topically because of its sensitizing

properties. Bacitracin and tyrothricin are relatively weak antibiotics and are usually ineffective when used on their own. Erythromycin has been little used topically because of the general policy throughout medicine to retain this antibiotic for organisms resistant to all others. It appears however, to be extremely effective and also non-irritant. The last antibiotic of this group is neomycin. It is effective, non-irritant on the whole, and not used systemically. Staphylococci rarely become resistant, but streptococci do. The main substances in the bacteriostatic group are chloramphenicol and the tetracyclines. The former is very active against staphylococci and there has been no increase in resistance to it over the last few years; cutaneous reactions, however, are more common. Staphylococcal resistance to the tetracyclines is increasing and they are widely used for systemic infections. For both of these reasons they should not be used topically unless there is some specific reason.

On the basis of this information neomycin emerges as the first choice in treating cutaneous infection. If this fails to control the condition and bacteriological investigation is unavailable, a change should be made to chloramphenicol. This antibiotic is also effective against most of the gram-negative organisms, although these are only present in pure culture in about 2 per cent. of skin infections. If there is bacteriological or clinical evidence of the presence of *Pseudomonas pyocyanea*, polymyxin should be used. This is available under various proprietary names ('polyfax', 'aerosporin') and should be reserved exclusively for use against this organism.

Many of the conditions with which the staphylococcus is associated are often recurrent, and fresh attacks may continue for months or years. Examples are boils and various types of folliculitis, the commonest being sycosis barbæ, seborrhœic dermatitis, intertrigo, infectious eczematoid dermatitis and secondarily infected pruritic conditions. Assuming there is no associated disease predisposing to infection, such as diabetes mellitus, the cause of the recurrences is the continued presence of the organism on the patients' uninvolved skin. The increasing knowledge of the epidemiology of staphylococcal infection in general has enabled a rational and largely effective approach to be made to the permanent eradication of these infectious dermatoses. Approximately 40 per cent. of healthy individuals carry pathogenic staphylococci in the anterior nares, and in certain sections of the population, such as doctors and nurses, the carrier rate may be as high as 80 per cent. Many of these people also carry the organism in the body folds, particularly the perineum, and in about 10 per cent. it is found in the latter area and not in the nostrils. With each episode of infection the bacterial population increases, not only in the sites of predilection, but also over a wide area of healthy skin around the lesion. The problem is therefore one of attempting to disinfect the whole of the patient's skin.

The nostrils should be treated with a locally applied antibiotic twice daily for a month. Neomycin is usually employed, in the form of a 0.5 per cent. ointment but, if there is clear evidence of a reservoir of infection in

the perineum or other intertriginous area, the lotion should be used to avoid undue maceration. The most effective agent for disinfecting the rest of the skin is hexachlorophane, which has a cumulative action, gradually building up a protective film on the skin. Its other great advantage is that it can be incorporated in soap without being destroyed. The suitably named 'cidal' soap is the brand most commonly employed and the patient should wash the whole of the skin daily for a period of two or three months. After the bath it is also wise to use a dusting powder containing an antibacterial agent, such as 1 per cent. chlorhexidine. This régime is effective in the majority of cases, but sometimes it is necessary also to arrange a course of ultra-violet rays two or three times a week for two months in generalized sub-erythema doses.

Attempts to increase or induce circulating antibodies against the staphylococcus by repeated injections of antitoxins or toxoids have proved disappointing and have largely been abandoned.

FUNGUS INFECTIONS

Chronic paronychia.—This is an indolent inflammatory condition of the skin around the base of the nails, which can persist for months or years. The causative factor is the yeast-like fungus, Candida (Monilia), a normal saprophyte of the gastro-intestinal tract, and infection occurs after defæcation (Whittle, Moffat and Davies, 1959). The predisposing causes are injury, maceration and poor peripheral circulation. Effective treatment depends upon the recognition of these facts and their eradication.

Nystatin is an antibiotic isolated from a soil streptomyces and has a specific action against Candida, and can be prescribed as an ointment, pessary or suspension (100,000 international units per g. or ml.) and as tablets for oral use (500,000 units per tablet). In chronic paronychia the ointment is applied under the affected nail-fold with an orange stick. The application should be used four times a day to ensure continuous action and gloves should be worn at night. The details of the malady should be explained to the patient and strict hygiene must be obtained with regard to defæcation. Continued maceration must be avoided by the wearing of suitable gloves for household washing, or a temporary change of occupation in the case of cooks and workers in the fruit-canning industry. Vasodilator drugs can be helpful if acrocyanosis or Raynaud's phenomenon is severe. The average patient recovers in two or three months. Occasionally, however, resistant cases are found. The cause appears to be continued reinfection and this may result from an undiagnosed Candida vaginitis which also requires treatment. If no other source of infection is found final cure can sometimes be obtained by decreasing the population of Candida in the gut. Two tablets of nystatin are given three times a day for two or three months. The drug is not absorbed and no side-effects have been reported.

The nail-plates are often involved in chronic paronychia. This may be secondary to the inflammation in the nail-forming epidermal cells, or due

to actual invasion of the nail-plate by Candida. In either event the condition clears up when the paronychia has been cured.

Ringworm.—The fungi which cause ringworm in man live in the keratin of skin, hair and nails. They are destroyed by the living cells which form this tissue and thus cannot invade. On the other hand, locally applied fungicides fail to cure because they cannot penetrate the keratin. Thus, the ideal anti-fungal agent would be one which, administered internally, could endow new keratin with the capacity to resist fungi. Such an agent appears at last to have been discovered.

Griseofulvin is an antibiotic obtained from a penicillium. It is given by mouth in 0.25-g. tablets, in a dose of 1 to 2 g. a day. It is well absorbed and rapidly excreted. In the concentrations obtained in man it is fungistatic rather than fungicidal and appears to obtain its curative effect by rendering the newly formed keratin resistant to fungi, the old keratin invaded before treatment was begun, being shed in the normal way together with the fungus. It is clear therefore that treatment has to be continued until all the infected keratin has been shed. In the case of finger-nails this may be as long as five or six months, the time taken for the keratin to travel from the base of the nail, where it is formed, to the distal end. In a nail of which only the distal portion is infected, the period of treatment will be proportionately less. Toe-nails take longer than finger-nails. Hair infected with *Microsporum audouini* can be recognized by its bright-green fluorescence when examined under Wood's light. By this method it can be seen that uninfected hair appears above the scalp about three weeks after administration of the drug has been started. Shaving of the head at this time should theoretically remove all the infected hairs, rendering the child uninfectious and able to return to school. Tinea corporis clears in about two weeks, but tinea pedis may take two or three months. Neither the optimum dosage nor the minimum period of treatment in the various types of infection, however, has yet been established.

Toxic reactions are uncommon. As very large doses in animals temporarily arrest mitoses, however, it is wise to perform repeated peripheral blood counts during prolonged therapy. So far, only urticaria-like drug eruptions and minor self-limited complaints of gastro-intestinal distress and headache have been reported. Nevertheless, as with any newly introduced drug, all patients should be carefully observed throughout treatment.

Griseofulvin is effective in favus but has no effect in Candida infections, pityriasis versicolor or blastomycosis.

References

Anderson, T. E., and Chalmers, D. (1959): *Brit. J. Derm.*, **71**, 214.
Inman, P. (1959): *Ibid.*, **71**, 211.
Lamont, I. C. (1959): *Ibid.*, **71**, 201.
Shelley, W. B., *et al.* (1958): *J. Amer. med. Ass.*, **167**, 1590.
Smith, J. G., Zawisza, R. J., and Blank, H. (1958): *A.M.A. Arch. Derm.* **78**, 643.
Whittle, C. H., Moffat, J. L., and Davies, R. A. (1959): *Brit. J. Derm.*, **71**, 1.

ADVANCES IN ENDOCRINOLOGY

By C. L. COPE, D.M., F.R.C.P.
AND M. T. HARRISON, M.B., M.R.C.P.
From the Department of Medicine, Postgraduate Medical School of London

FOR the purpose of this review we have selected five subjects for discussion: radio-iodine therapy, the newer corticosteroids, iatrogenic female pseudo-hermaphroditism, human growth hormone, and the treatment of cancer of the breast by hypophysectomy.

RADIO-IODINE THERAPY

Hyperthyroidism.—The fact that iodine is preferentially concentrated in thyroid tissue makes it relatively easy to apply a destructive dose of irradiation to the gland by administration of radioactive iodine (I^{131}). The quantity needed is infinitesimal, it is given by mouth, and 80 per cent. or more of the dose will usually be concentrated in the thyroid. In many respects this provides an ideal method of obtaining a thyroidectomy without the hazards of a surgical operation. But the more rapid extension of the method is at present hampered by our lack of sufficiently precise knowledge of the deleterious effects of radiation, especially as regards the possible initiation of a carcinoma. Because of the intense concentration of iodine in the thyroid gland it is possible to give the gland a fully destructive dose with only a very small exposure to irradiation of the other tissues of the body. Risk to other tissues such as the gonads is therefore small although perhaps not yet quite negligible, since the question of whether or not there is a threshold to the damaging dose of irradiation or whether the effects of small doses are cumulative is not yet decided.

The main cause for hesitancy is the possibility of malignant development in the thyroid tissue itself. Since this may conceivably occur as long as twenty years after the exposure, and few patients have been treated for more than ten years, it follows that sufficient experience cannot yet have been accumulated on which the precise magnitude of this risk can be reliably estimated. Until such evidence is available caution is desirable although it must be admitted that no case of carcinoma of the thyroid has yet been clearly attributable to I^{131} therapy. It is generally considered unwise at present to give it to children, to pregnant mothers or even to women in the child-bearing age unless special reasons exist for not employing the usual antithyroid drugs or surgical ablation.

The treatment is particularly useful for thyrotoxic persons over the age of 50, and also for those above or even below this age who are poor operative risks. As more evidence is gradually accumulated about the safety of this treatment it is likely to be considerably extended, since nothing is involved for the patient save the drinking of one or two doses of a tasteless aqueous

solution. In many cases admission to hospital will be found unnecessary. The dose required, which should be chosen by an expert in radiotherapy, is not critical since glands vary considerably in their sensitivity to the drug. If incomplete suppression of the gland is achieved, a second dose can easily be given and, if the thyroid is too heavily suppressed, causing hypothyroidism, supplements of thyroid hormone will readily restore the patient to a euthyroid state.

Two extensive reports of the results of radio-iodine treatment have been published in this country from the large Sheffield clinic.

In the first report (Blomfield *et al.*, 1955) 140 cases are reviewed. Postoperative myxœdema was encountered in 12 per cent. but some of these were due to inexperience. Complications were few and not certainly related to the radio-iodine treatment, although various rheumatic symptoms which usually responded to aspirin were found in about 10 per cent. Adverse effects on any exophthalmos present were rare.

In a later review of 500 cases treated in this clinic (Blomfield *et al.*, 1959) 59 per cent. became euthyroid at the first treatment and a further 21 per cent. after a second treatment. Hypothyroidism occurred in 12 per cent., being thus unchanged from the earlier review. In the whole group relapse was uncommon, only 27 cases relapsing after a successful first course of treatment with return to apparently euthyroid state.

Toxic nodular goitres seem to have responded just as well as diffuse goitres, and early fears that radio-iodine treatment would prove unsuitable if tracheal compression were present seem to be unfounded. Although surgery is still necessary if rapid relief of the compression is an urgent need, radio-iodine can profitably be used if the compression is less severe.

Pochin (1958) has well summarized British views on the place of radio-iodine in thyroid therapy. Representative American experience is similar and has been well reviewed by Chapman and Maloof (1955), of Harvard, in a survey based on 500 treated cases followed for up to seven years. They note that, whilst full clinical response often occurred in about two months, it was often considerably delayed in thyrocardiacs, even up to a year. This slow response may prove a disadvantage in some cases. Although suppression of thyroid activity may be speeded by an antithyroid drug, this is likely to reduce further the efficacy of the radio-iodine therapy. In spite of this, radio-iodine would seem to be the treatment of choice in the majority of thyrocardiac subjects.

Carcinoma of the thyroid.—If every thyroid carcinoma continued to concentrate iodine, radio-iodine therapy would be an ideal method of treating this cancer. Unfortunately this is not so, and a large number, especially the more anaplastic tumours, fail to take up sufficient radio-iodine to receive an adequate dose of radiation. The greater the tendency to follicle formation of the thyroid tumour, the greater the likelihood, in general, of response to radio-iodine. The proportion of cases which will take up radio-iodine can be increased by preliminary stimulation of the gland. Although injection of thyrotropic hormone will do this, a more practical method is to induce in the

patient a state of myxœdema. This is best done by surgical ablation of as much thyroid tissue as possible but, if this proves difficult, a preliminary radio-iodine treatment of the thyroid gland itself will be needed. Several weeks of resultant hypothyroidism may be needed before the avidity of the tumour tissue for iodine is increased.

Whilst cure cannot be hoped for, great relief of symptoms may be expected in a good proportion of cases, and many metastases may be made to shrink greatly or even apparently disappear. Experience with over 110 patients treated for carcinoma of the thyroid has been reviewed by Gwen Hilton and her colleagues at University College Hospital, London (1956). Of this series, 73 were given the full course of radio-iodine treatment. Twenty of 24 were still alive at three years and five of seven still alive five years after treatment. Anaplastic carcinomas did much less satisfactorily than the better-differentiated tumours. Several cases with metastases in mediastinum or lungs have survived three or more years, but the prognosis of those with metastases in bones seems to be poor.

NEWER CORTICOSTEROIDS

During the past few years strenuous and successful efforts have been made to modify the hydrocortisone molecule in such a manner that desirable effects are enhanced and undesirable ones minimized. It is still not completely clear how well this can be done and further developments may confidently be expected. It seems that the so-called anti-inflammatory or anti-rheumatic effects—the main therapeutic actions—are closely allied to the so-called glucogenic properties. It is likely therefore that the desirable therapeutic actions will prove inseparable from some other actions which may cause undesirable side-effects, such, for instance, as the impaired resistance to infection, the liability to progressive osteoporosis and the diabetogenic tendency. On the other hand, the well-known properties of the steroid deoxycortone acetate show clearly that the electrolyte-controlling properties of the molecule are separable from and independent of the anti-inflammatory, for this steroid, so potent in electrolyte control, has no anti-rheumatic action at all.

A variety of ways has now been found of varying the electrolyte-controlling action independently of the anti-inflammatory. Thus, the attachment of an atom of fluorine, or other halogen, to the 9 carbon atom of hydrocortisone greatly enhances the electrolyte effect. Whilst this drug still retains its anti-rheumatic effect it cannot be used easily for this purpose because of the excessive sodium and water retention it causes, but such a steroid has particular use in the treatment of Addison's disease. Attachment of a methyl group to the 2 carbon atom also enhances electrolyte activity and, if both modifications are introduced together, a high degree of electrolyte-controlling activity is achieved relative to the anti-inflammatory effect. For the treatment of many disorders, however, the electrolyte

effect is a particularly undesirable feature. Its elimination without destruction of the anti-rheumatic effect is thus an aim of great clinical importance.

Attachment of a methyl group to the 6 carbon in prednisolone confers some benefit including mild reduction in electrolyte effect (Liddle, 1958), but the change has been most dramatically achieved by modifications made on the 16 carbon atom of the hydrocortisone or prednisolone molecule. In the newer steroid, triamcinolone, a hydroxyl group is attached at this point, and this compound also possesses the fluorine modification mentioned above. The effect of the 16-hydroxyl group is almost completely to remove the sodium-retaining and potassium-losing effects without reducing the anti-inflammatory effect. Triamcinolone is as potent in therapy therefore as prednisone and is used in similar dosage but is freed from the undesirable sodium retention. A still more recent modification has been the replacement of the 16 hydroxyl in the triamcinolone molecule by 16 methyl, yielding a compound to which the name, dexamethasone, has been given. In this compound, also, the electrolyte effects are almost eliminated, but the methyl group slows metabolism of the compound and thereby increases its therapeutic action. Dexamethasone is about six times as potent therapeutically as triamcinolone or prednisone (Boland, 1958). This increased potency is not of itself necessarily an advantage, although it may be hoped that the smaller dose needed will reduce liability to peptic ulceration.

These newly introduced steroids thus offer considerable advantages over their predecessors for many purposes. Because of its earlier introduction experience is greater with triamcinolone. This is certainly an effective therapeutic agent but some toxic effects are still present (Hart *et al.*, 1958). Mooning of the face still occurs, and gastric symptoms may still arise as may peptic ulceration, although it is possible that the tendency to this is reduced. Unlike some of its steroid predecessors, triamcinolone may cause headache and dizziness, sufficient occasionally for a change to another steroid to be desirable. Euphoria does not seem to occur, but anorexia may develop. Weakness and muscle fatigue may become marked in persons on the drug (Dubois, 1958), and a peculiar form of generalized myopathy has been described as a complication (Williams, 1959). The fluorine in the molecule may prove to be the cause of this myopathy for it has been seen also with 9α-fluorohydrocortisone (fludrocortisone) (MacLean and Schurr, 1959). On the credit side is the fact that sodium and fluid retention is almost completely absent with triamcinolone. Thus, steroid hypertension or steroid œdema developed on one of the older steroids may subside completely on switching to this steroid in therapeutically equivalent dosage. Potassium loss also is a negligible hazard with this drug.

Because of its more recent introduction, less experience has been obtained with dexamethasone. The six-fold increase in therapeutic potency is not of itself an advantage unless it results in a reduction of side-effects. We have not ourselves observed with dexamethasone the toxic effects seen with

triamcinolone. Appetite tends to increase rather than diminish; it seems likely that peptic ulceration will occasionally occur and some other side-effects associated with the anti-inflammatory action such as poor resistance to infection are likely to continue with this steroid. With this very potent steroid, osteoporosis, too, is likely to prove a real risk for it appears to cause a more significant and sustained negative calcium balance than does prednisone (Bunim *et al.*, 1958).

Both these steroids, however, represent major advances in steroid therapy. Although they may still have side-effects, they are the steroids of choice in all conditions, such as cardiac failure, œdema or ascites, where further sodium retention is highly undesirable, yet corticosteroid therapy is called for.

Much progress has also been made in the development of potent anabolic steroids with reduced androgenic properties. This has been well reviewed in its theoretical and clinical aspects by Foss (1959).

IATROGENIC FEMALE PSEUDOHERMAPHRODITISM

The clinical condition of female pseudohermaphroditism associated with evidence of adrenal hyperplasia and with abnormal adrenal steroid metabolism is now well known, although the explanation of the peculiar and varied metabolic defect is probably not as simple as was at first thought. But there is another group of clinically rather similar cases where there is no associated adrenal hyperplasia. Such cases, though rare, are of some practical importance. Whilst varied causes of the condition may be found, there is now much evidence that many such cases are caused by vigorous hormone treatment of the mother during her pregnancy. In theory the condition could arise from any strongly virilizing cause in the mother during her pregnancy and two cases due to an arrhenoblastoma have, in fact, been recorded, but a far commoner cause is now found to be the administration of an androgenic steroid to the pregnant woman. With the rapidly extending use of potent steroids for many purposes, this is likely to become a more common danger.

Wilkins and his colleagues (1958) have collected 21 such cases and found a further six reported in the literature. Several examples have already been seen in this country, notably by Moncrieff (1958) and by Black and Bentley (1959).

The most commonly administered causative androgen has been ethisterone, but methyltestosterone and methylandrostenediol (methandriol) have both produced the syndrome, and it is probable that other causative steroids will be recognized. The more recent steroid, 17-ethinyl-19-nortestosterone (norethisterone), used as an oral progestin, is likely to be one of these.

Some clinical differences from the congenital form of adrenal hyperplasia are apparent and enable the syndrome to be recognized. Although the phallic enlargement in these cases is marked, it is often somewhat less than is usually seen in the classical adrenogenital syndrome. Fusion of the

labia minora occurs but may be only partial. The cases all show a female type of nuclear chromatin in skin cells. They differ from the true congenital cases in having a normal level of urinary 17-ketosteroids and in the absence of pregnantriol from the urine. These two tests are of major diagnostic value.

In some cases the causative steroid therapy has been strongly indicated by associated disease in the mother, as, for instance, by sarcoma of the breast or because of threatened abortion or frequent past miscarriages. In other instances, however, the indications have been far more slender as, for instance, to treat alopecia, 'weakness and low blood pressure' or pruritus. The fact that the causative factor is a temporary one means that the prognosis is much better than in the cases with an inborn error of metabolism. Surgical correction of the defect is fairly simple even in the more severe cases. Many pregnant women are given androgenic steroids without damage to the fœtus, so that it would seem that a second factor is needed to produce the fœtal masculinization. Because of this the risks of giving these steroids is relatively small and Wilkins points out that there is inadequate reason to abandon them in the treatment of habitual or threatened abortion. It would seem most desirable, however, to be very cautious about giving them to the pregnant mother when the indications are more slender ones, and to avoid the use of such steroids, if at all possible, during the first twelve weeks of pregnancy.

HUMAN GROWTH HORMONE

The normal growth of children is dependent upon many factors, including the pituitary growth hormone, the thyroid hormone, and androgens secreted by the adrenal cortex and the testes. In children with panhypopituitarism all these hormones are absent or deficient and dwarfism results. Treatment with thyroid hormone alone does not produce normal growth in these children, and androgens have the disadvantage of accelerating skeletal maturation as well as promoting growth, so that the epiphyses of the long bones fuse with the shaft preventing further growth in length. Growth hormone prepared from the pituitary glands of slaughterhouse animals has been available for some years, but such preparations are not active in man.

In 1957, Raben reported the isolation of growth hormones from the pituitaries of humans and of rhesus monkeys, the latter being available because the animals were being used in the preparation of poliomyelitis vaccine. The hormone from both these sources was found to be active in man.

It is extracted from the acetone-dried pituitary powder, and separated from the other pituitary hormones by adsorption of the latter on oxycellulose. Depending upon the method of extraction the yield from one human pituitary gland is from 1 to 4 mg. of growth hormone.

Small amounts of human growth hormone have now been prepared and their metabolic effects in man studied.

Raben (1958) has treated a 17-year-old hypopituitary dwarf with human growth hormone for ten months.

A dose of 2 mg. three times a week by injection produced a gain in height of 2.1 inches (53 mm.), compared with a growth rate of 0.5 inch (12.6 mm.) a year before treatment. There was no increase in bone age and no sexual maturation during treatment. A rise was noted in hæmoglobin, serum phosphate, and alkaline phosphatase.

Other observations on the acute effects of human growth hormone have been reported (e.g. Beck *et al.*, 1958; Ikkos *et al.*, 1958; Medical Research Council, 1959). Retention of nitrogen, phosphorus, sodium, potassium, and magnesium occurs following a single large dose, reflecting the increased protein anabolism. There is sometimes an increased excretion of calcium in the urine; this is unexplained, but recalls the hypercalciuria and osteoporosis that are seen in some patients with acromegaly. A rapid rise in the plasma unesterified fatty-acid level occurs following growth hormone injection, which is probably due to mobilization of neutral fat. This may prove to be a sensitive index of the activity of the hormone.

Long-term studies of human growth hormones are now in progress in several centres to assess the effect of prolonged treatment in children with hypopituitarism. Whether the hormone will prove of value in other conditions, by virtue of its anabolic effects, remains to be seen. At present the amounts of hormone available are small and it will probably be a long time before sufficient quantities can be produced for general use. There seems no doubt, however, that we have here a new and potent therapeutic substance.

TREATMENT OF BREAST CANCER BY HYPOPHYSECTOMY

Many cancers of the breast depend upon the presence of hormones for their growth, and removal of certain endocrine glands often leads to arrest of growth and even temporary remission of these tumours. It is not known exactly which hormones are concerned in the development of breast cancer or how they affect it, but it seems that œstrogens and progesterone, growth hormone and prolactin (lactogenic or luteotrophic hormone) are necessary in order for the breast cancer cells to survive, at least during certain stages in their development. Moreover, there is probably a synergistic action between the ovarian (or adrenal) œstrogens and the pituitary hormones, so that the presence of both groups of hormones is necessary for survival of the dependent tumour cells.

Removal of the ovaries and adrenal glands will produce a remission in hormone-dependent breast cancer, and the results of these operations were reviewed in *The Practitioner* earlier this year (Pearson and Rhoads, 1959). Removal of the pituitary gland, however, has several advantages over the other operations. It removes not only the stimulus to œstrogen production but also the growth and lactogenic hormones which are also concerned in tumour growth. Moreover, the salt-retaining hormone, aldosterone, is still

produced by the adrenal glands after hypophysectomy, and control of the patient is therefore easier. Thirdly, adrenalectomy is a major procedure, not always feasible in very ill patients with disseminated cancer, and sometimes the adrenal glands are so involved in metastatic tumour tissue that total removal is impossible.

Total hypophysectomy for breast cancer was first carried out in 1952 by Luft and his colleagues, using an intracranial approach. This method, although still widely used, is a major procedure, and there is a risk of damage to the optic nerves or tracts, and infarction of the frontal lobes as a result of disturbance of their venous drainage. Because of these disadvantages, Forrest and Peebles Brown, in 1955, devised an alternative method for destruction of the pituitary gland. Seeds of radon were introduced into the gland by means of a cannula inserted into the pituitary fossa through the nose and sphenoidal sinus. This is a minor and relatively rapid procedure, involving little stress to the patient, who may be severely ill as a result of his cancer. Its disadvantages lie in the risk of irradiating other nearby structures: the optic chiasma, leading to visual field defects or blindness; the diaphragma sellæ, which may lead to rhinorrhœa and meningitis; and the oculomotor nerve, leading to paralysis of eye movements and diplopia. These dangers have been lessened by the substitution of yttrium (Y^{90}) for radon. Yttrium emits beta rays, which have a low penetrating power compared with the gamma rays emitted by radon, and so adequate irradiation of the pituitary gland is achieved using yttrium without effects on neighbouring structures.

Several advances have recently been made in the technique of pituitary implantation with radioactive material. Bauer (1957) approaches the pituitary fossa via the transethmoidal route, instead of through the nasal cavity and sphenoidal sinus. This allows easier access to the fossa and the seeds may be placed more accurately. Forrest and his colleagues (1958) have devised a screw which holds the radioactive seed in position inside the fossa, and also seals the hole made in the floor of the fossa, thus preventing rhinorrhœa. Thirdly, Bloch and Joplin (1959) have clearly defined for the first time the radiological anatomy of the pituitary fossa and its relations to the optic chiasma, oculomotor nerve and diaphragma sellæ. With a knowledge of these relations, it is possible to implant the radioactive seeds sufficiently far from these structures to ensure that they will not be damaged by irradiation, as Fraser and his colleagues have shown (1959). It may be that these discoveries will lead to the evolution of an ideal method for pituitary ablation, and make this a feasible procedure in the most severely ill patient, with little risk of undesirable side-effects and a good chance of remission of the cancer.

In the largest reported series of patients with breast cancer treated by hypophysectomy, employing craniotomy, a remission was obtained in about half the patients, longer in duration than that obtained from combined

ovariectomy and adrenalectomy (Pearson and Ray, 1959). Hypophysectomy was found to be of benefit in six patients who had already undergone ovariectomy and adrenalectomy. Whether hypophysectomy is of value in other forms of cancer remains to be seen: preliminary observations suggest that cancer of the prostate may also respond to this therapy.

References

Bauer, K. H. (1957): *Arch. klin. Chir.*, **287,** 17.
Beck, J. C., McGarry, E. E., Dyrenfurth, I., and Venning, E. H. (1958): *Ann. intern. Med.*, **49,** 1090.
Black, J. A., and Bentley, J. F. R. (1959): *Lancet*, **i,** 21.
Bloch, H. J., and Joplin, G. F. (1959): *Brit. J. Radiol.*, **32,** 527.
Blomfield, G. W., Jones, J. C., Macgregor, A. G., Miller, H., Wayne, E. J., and Weetch, R. S. (1955): *Brit. med. J.*, **ii,** 1223.
——, Eckert, H., Fisher, M., Miller, H., Munro, D. S., and Wilson, G. M. (1959): *Ibid.*, **i,** 63.
Boland, E. W. (1958): *Calif. Med.*, **88,** 417.
Bunim, J. J., Black, R. L., Lutwak, L., Peterson, R. E., and Donald Whedon, G. (1958): *Arthritis and Rheumatism*, **1,** 313.
Chapman, E. M., and Maloof, F. (1955): *Medicine* (*Baltimore*), **34,** 261.
Dubois, E. L. (1958): *J. Amer. med. Ass.*, **167,** 1590.
Forrest, A. P. M., and Peebles Brown, D. A. (1955): *Lancet*, **i,** 1054.
——, Blair, D. W., and Valentine, J. M. (1958): *Ibid.*, **ii,** 192.
Foss, G. L. (1959): *The Practitioner*, **182,** 235.
Fraser, R., Joplin, G. F., Laws, J. W., Morrison, R., and Steiner, R. E. (1959): *Lancet*, **i,** 382.
Hart, F. D., Golding, J. R., and Burley, D. (1958): *Ibid.*, **ii,** 495.
Hilton, G., Pochin, E. E., Cunningham, R. M., and Halnan, K. E. (1956): *Brit. J. Radiol.*, **29,** 297.
Ikkos, D., Luft, R., and Gemzell, C. A. (1958): *Lancet*, **i,** 720.
Liddle, G. W. (1958): *Metabolism*, **7,** 405.
Luft, R., Olivecrona, H., and Sjögren, B. (1952): *Nord. Med.*, **47,** 351.
MacLean, K., and Schurr, P. H. (1959): *Lancet*, **i,** 701.
Medical Research Council (1959): *Ibid.*, **i,** 7.
Moncrieff, A. (1958): *Ibid.*, **ii,** 267.
Pearson, O. H., and Ray, B. S. (1959): *Cancer* (*Philad.*), **12,** 85.
——, and Rhoads, C. P. (1959): *The Practitioner*, **182,** 687.
Pochin, E. E. (1958): In 'Modern Trends in Endocrinology', edited by H. Gardiner-Hill, London, p. 46.
Raben, M. S. (1957): *Science*, **125,** 883.
—— (1958): *J. clin. Endocr.*, **18,** 901.
Wilkins, L., Jones, H. W., Holman, G. H., and Stempfel, R. S. (1958): *Ibid.*, **18,** 559.
Williams, R. S. (1959): *Lancet*, **i,** 698.

ADVANCES IN THE TREATMENT OF RENAL DISEASE

By G. A. SMART, M.D., B.Sc., F.R.C.P.
Professor of Medicine, University of Durham

SINCE this subject was last reviewed in 'Advances in Treatment' (Fishberg (1955)) it would be fair to say that there have been no spectacular or radical advances in the treatment of renal disease. The period has been one of consolidation, of improvement in the use of known therapeutic measures and agents, and, above all, in the greater precision with which these measures can be used. An important contribution to this precision has been made by the introduction of needle biopsy of the kidney.

ACUTE RENAL INSUFFICIENCY

This occurs when the secretion of urine falls below 300 to 400 ml. a day. The patient may not be absolutely anuric and it is important to realize that oliguria may easily be overlooked. If oliguria is present it is often assumed that this is due to dehydration; it may, however, be due to reversible renal damage and an error in this differentiation can have serious consequences. During this time there may be serious nitrogen retention and no regulation of electrolyte concentration. Moreover, if normal quantities of water are taken, serious overhydration may occur. The phase of oliguria may be followed by one of high urinary output. Nevertheless, this urine may be dilute, so that elimination of nitrogenous waste products is still inadequate and, perhaps even more important, electrolyte regulation remains seriously impaired. If the nitrogen retention and electrolyte abnormality are only noticed during the diuretic phase, the patient may be thought, erroneously, to be suffering from chronic renal failure.

In order therefore that such errors may be avoided, it is important that the urinary output every twenty-four hours should be accurately measured in all patients who have been in any situation likely to be followed by anuria or oliguria. The most important of these conditions are: (a) toxæmia of pregnancy, (b) obstetric accidents or hæmorrhage, (c) trauma, particularly if this has been associated with blood loss, extensive tissue damage or shock with marked fall in blood pressure, (d) any period of prolonged hyptotension from whatever cause, (e) therapeutic accidents such as mismatched blood transfusions, (f) any major surgical procedure. It should also be noted that there may be a considerable delay before certain nephrotoxic substances (e.g. carbon tetrachloride) produce their effect on the kidney; thus the urinary output of any patient who has been subjected to important amounts of such a substance should be measured each day for at least three weeks.

If oliguria or anuria should develop it is important that the conservative measures developed by Borst (1948), and Bull, Joekes and Lowe (1949), and reviewed by Bull (1955) and by Fishberg (1955) should be taken immediately. The matter is so important that repetition of the principles involved will not be amiss; they all derive from the fact that the kidney can no longer excrete waste products nor can it regulate water and electrolyte excretion so as to maintain a physiological 'milieu interieur' in spite of variable intake.

DIET AND FLUID CONTROL IN ACUTE RENAL INSUFFICIENCY

The end-products of nitrogenous metabolism occur inevitably, but steps should be taken to reduce them to a minimum. Hence only carbohydrate and/or fat is given as a source of calories. Fat emulsions by intragastric drip are no longer used by many workers because there is a distinct tendency for them to cause gastro-intestinal disturbances, including diarrhœa. Most workers now give glucose in quantities from 100 g. to 300 g. a day either by mouth or by a catheter introduced into a great vein. Some 500 to 600 ml. of water are produced daily by metabolic processes and thus, since it is of great importance to avoid overhydration, only about 400 to 500 ml. a day may be given if there is complete anuria and no water loss except by evaporation. Hence the solutions of glucose to be administered must be 25 per cent. or more in strength. These tend to cause vomiting if given by mouth and they tend to cause thrombosis when given intravenously. For this reason, if a patient is unable to take the glucose by mouth it should be given through a long catheter inserted into a large vein, preferably the inferior vena cava where, owing to the large volume of blood flow, rapid dilution of the glucose can take place. In this way the risks of thrombosis and embolism are minimized, but serious complications of this sort may still occur (Taylor, 1959; Chambers and Smith, 1957; Barr and Chambers, 1958; Shaw and Mair, 1954; Shaw, 1959). Such a strict régime may not be so necessary if the patient is being treated in a unit where an artificial kidney is available.

Infection of any sort results in a great increase in cellular metabolism and therefore must be avoided. Patients with anuria should be 'reverse' barrier nursed—to prevent them from catching any infection, rather than the more usual reason, to prevent infection spreading from the patient.

The breakdown of body protein may be decreased, particularly in patients with oliguria following an obstetric catastrophe, by means of protein anabolic substances. McCracken and Parsons (1958) have advocated the use of 17-ethyl-19-nortestosterone (norethandrolone) in such patients and have shown that in doses of 80 mg. a day protein catabolism was reduced by an average of 70 per cent.

As outlined above, water must only be given in small quantities of about 400 ml. daily, if the only loss is that which occurs by evaporation. If other

water loss occurs, as, for example, in the presence of diarrhœa or fluid from fistulæ or wounds, then the volume lost in this way should be added to the basic 400-ml. requirement. A practical way of ensuring a proper balance is to weigh the patient daily, a loss of some 300 to 400 g. a day being allowed for the inevitable tissue breakdown.

ELECTROLYTE CONTROL IN ACUTE RENAL INSUFFICIENCY

With regard to electrolytes, none should be given unless there is a loss, and in this event only in amounts appropriate to maintain normal concentrations in the body fluids. With the inevitable breakdown of tissue there is a continuous release of potassium into extracellular fluid and the concentration therein may soon reach dangerous levels. If it is necessary to deal with this as an emergency, insulin and glucose may be given intravenously, a measure which causes the ion to enter cells and so reduces extracellular concentration. A further measure which can be undertaken is to give a suitable resin, either by mouth or by enema. This adsorbs potassium and so removes it from the body, but is not by itself sufficient, if the high potassium concentration is in proportion to the increase in concentration of nitrogenous waste products in the plasma. In these circumstances some form of artificial hæmodialysis is required. The use of the artificial kidney has been reviewed many times (Kolff and Berk, 1944; Merrill, 1950; Skeggs and Leonard, 1948; Kolff, 1957; Parsons and McCracken, 1959; Alwall, 1947). Whatever the type used, a large team is required, not only because of the complexity of the technical problems involved, but because of the seriously ill state of so many anuric patients. The procedure can be life-saving in patients with reversible renal failure; it may also be a means of prolonging useful life, even in some patients who have underlying chronic renal failure, but who have become acutely uræmic because of some incidental but short-lived episode which has increased the renal failure to a fatal degree.

Dialysis has also been carried out by intestinal lavage and by running appropriate fluid through the peritoneal cavity. There were many disadvantages to these techniques and they have largely been discarded. Recently, however, it has been claimed by Maxwell and his colleagues (1959) and by Doolan and his colleagues (1959) that *intermittent* dialysis across the peritoneum can be successfully and easily carried out by introducing 2 litres of a 5 to 7 per cent. dextrose solution, with appropriate electrolytes, tetracycline, and heparin, into the peritoneal cavity, leaving it there for one to two hours and then running it off by gravity. The process is repeated a large number of times. It would appear to be much more easily and cheaply carried out than dialysis by means of an artificial kidney, but it is not such an efficient procedure.

PYELONEPHRITIS

Since the classical paper by Weiss and Parker (1939) it has become in-

creasingly recognized that chronic pyelonephritis is a common condition, often undiagnosed during life.

Platt and Davson (1950), who studied 188 cases of renal disease, found pyelonephritis to be the commonest diagnosis, 26 patients having the condition; Ellis Types I and II nephritis were the diagnoses in 23 and 25 patients respectively. These patients were of course somewhat selected in that they came within the purview of physicians with a particular interest in renal disease. Studies of consecutive necropsies by Raaschou (1948) have shown pyelonephritis to be present in 6.3 per cent. The condition was also found by him to be the commonest cause of uræmia. Similar figures have been obtained in Prague (Brod, 1956). Jackson and his colleagues (1957) found pyelonephritis to be present in 9 per cent. of 4,425 consecutive necropsies and in 3 per cent. the lesion was of major pathological importance.

It is thus of great importance to prevent, where possible, the onset of this serious condition or to recognize the earliest manifestations, for, once established, it is very difficult to treat satisfactorily.

Infection of the urinary tract, especially when this is associated with anatomical abnormalities, or obstruction, or with diabetes mellitus, may give rise to pyelonephritis. Once this has occurred the resultant scarring and obstruction to urinary flow down the tubules almost certainly renders the kidney particularly liable to infection from blood-borne organisms (Gorrill, 1958; De Navasquez, 1958; Talbot, 1958). It is thus of the greatest importance to avoid producing urinary infections by instrumentation, to recognize infection of the urine as soon as possible and to treat it seriously and thoroughly. To regard 'pyelitis' as almost a normal phenomenon of, for instance, pregnancy is dangerous and thoroughly reprehensible.

It has been well established that the early stages of uncomplicated infections of the lower urinary tract can usually be treated effectively by mandelic acid or methenamine mandelate but, if there is any evidencé that such therapy is not fully effective, appropriate doses of a chemotherapeutic agent or an antibiotic, to which the organism has been shown to be sensitive, should be used (Kass, 1955; Jackson, Poirier and Grieble, 1957). Nitrofurantoin is proving to be a useful chemotherapeutic agent for most urinary infections other than those due to *Pseudomonas pyocyanea* (Fairbrother, 1957). McGeown (1956) has used this substance successfully in high dosage (10 mg./kg./24 hours) in the presence of renal calculi. Nausea and vomiting are the main side-effects and these are minimized if the drug is given with meals. It has been pointed out that once the kidney is infected the lesion may be interstitial and that the dose of antibiotic should be sufficient to cause an effective concentration in the tissues rather than in the urine (Birchall and Alexander, 1950). In general, treatment of established pyelonephritis is most unsatisfactory, new and resistant organisms making their appearance soon after one infection has been apparently cleared. Prolonged treatment for periods of three weeks to six months has thus been advocated, but it has still to be shown that this will give over-all satisfactory results (Birchall and Alexander, 1950; Stansfeld and Webb, 1954).

The prevention of urinary infection has been mentioned and there is a good deal of evidence that the practice of catheterization is not altogether as harmless as might have been supposed (Monzon, *et al.*, 1958; Guze and Beeson, 1956; Beeson, 1956). Unless there are definite and pressing indications for the procedure it should be avoided. Urinary specimens for bacteriological examination are best collected by the mid-stream technique in the male and a similar method has been devised for the female (Hart and Magee, 1957).

Finally, it should be pointed out that chronic pyelonephritis may be quite unsymptomatic and may not be associated with organisms in the urine, although there are usually more than 100,000 per ml. (MacDonald, *et al.*, 1957). Renal biopsy may show that the specimen obtained is infected, or urine, previously sterile, may contain organisms after the biopsy has been performed (Williams, 1958). Such 'silent' pyelonephritis may be the cause of asymptomatic albuminuria (Pollak, *et al.*, 1958). Appropriate antibiotic therapy may sometimes prevent the onset of progressive renal destruction in such patients.

Kark and his colleagues (1955) have described a few patients in whom they found, by means of renal biopsy, that the kidneys were infected, although the histological appearances were not those of pyelonephritis. They suggest the name 'subacute bacterial nephritis' for the condition and point out that at present a diagnosis can only be established by renal biopsy. Appropriate chemotherapy has apparently cured the condition.

THE NEPHROTIC SYNDROME

The introduction of needle biopsy of the kidney by Iversen and Brun (1951) and its development by Kark and Muehrcke (1954) have added greatly to the precision whereby the underlying cause in a given case of the nephrotic syndrome can be determined. In this way therapy can be much more rational and the results more accurately predicted. The aims in treating patients suffering from the nephrotic syndrome are to reverse the renal lesion if this is possible, to produce a diuresis, and to render the patient free from œdema. There seems to be little doubt that in appropriate cases the use of corticotrophin, cortisone, prednisone, or allied steroids, in adequate dosage can produce a complete remission, resulting not only in a diuresis but in a complete cessation of the proteinuria. The essential glomerular lesions in such cases may be ultramicroscopic and only detectable by the electron microscope. They consist of an absence of the normal 'foot processes' which are formed from the epithelial cytoplasm and, instead, the presence of sheets of epithelial cytoplasm covering the capillary loops. The basement membrane is also somewhat thicker than normal (Farquhar, *et al.*, 1957) and after treatment with prednisolone the appearances have been found to have reverted to normal.

On the other hand, renal lesions such as amyloid deposits, glomerular

changes associated with disseminated lupus erythematosus, or diabetes mellitus, do not respond to therapy with corticosteroid compounds, nor does the nephrotic syndrome resulting from thrombosis of the renal vein. When glomerular changes are present which are characteristic of Ellis's type II nephritis a diuresis may be produced, together with a considerable reduction in the daily urinary loss of protein. Renal biopsy is often essential to determine which of these lesions is present.

CORTICOSTEROIDS IN THE NEPHROTIC SYNDROME

The natural history of the nephrotic syndrome is, as one would expect of a heterogeneous collection of entities, characterized by its unpredictability. Precision in diagnosis is only now becoming possible and it is still too early to be precise about the course of some of the entities giving rise to the nephrotic syndrome—particularly those with glomerular lesions which appear to be potentially reversible. Excluding disseminated lupus erythematosus, amyloid disease, diabetic intercapillary glomerulo-sclerosis, thrombosis of the renal vein, and tubular lesions produced by toxic substances, and other rare causes of the nephrotic syndrome, the treatment of choice is either corticotrophin, cortisone or a related steroid. Without extensive controlled trials it is idle to assert better therapeutic effects for one as compared with another, but prednisone, prednisolone and their derivatives, such as dexamethasone, have the advantage that there is little sodium retention and potassium loss. These substances should be given in fairly large doses (equivalent to about 200 to 300 mg. of cortisone a day) for up to three weeks in the first place. They should be accompanied by penicillin, since nephrotic patients are in any case liable to contract infections, and careful and frequent estimations of serum electrolytes (particularly sodium and potassium) should be carried out. Such therapy is likely to be unsuccessful or even dangerous in patients having an important degree of hypertension or evidence of significant renal failure. It has been stated that a diuresis occurs only when the drug is withdrawn, but this is incorrect. Diuresis will occur, if it is going to, during the therapy provided this is continued for a sufficiently long time. Diminution or cessation of proteinuria may also occur and usually a maximum effect will have been obtained by about three weeks (Charlton, *et al.*, 1958). It is felt by many workers that the patient should be kept thereafter on smaller doses of the steroid (Lange, *et al.*, 1953; Merrill, *et al.*, 1954; Debré, *et al.*, 1956).

My own practice is to keep those of my patients who respond only partially (i.e. who have a diuresis, but who are left with residual proteinuria) on continuous steroid therapy, but those who are rendered free from proteinuria are taken off all therapy. They are taught to test their own urine either with salicylsulphonic acid or with 'albustix' and to report immediately if there should be any return of protein. When this persists for more than a few days, even though only small quantities are present

and there is no œdema, a further course of therapy with an appropriate steroid is given. This almost always results in a further complete remission of the proteinuria.

ALBUMIN AND DIURETICS IN THE NEPHROTIC SYNDROME

For those patients with irreversible renal lesions it is necessary by more indirect means to lessen or to abolish the œdema. A diet high in protein has long been advocated to make up for the loss in albumin in the urine. This certainly may ensure that adequate quantities of appropriate amino-acids are supplied, but it has been shown that the rate of production of albumin in nephrotics is much greater than normal and it may well be at a maximum. It would seem to be more useful therefore to give ***human sodium-free albumin*** intravenously. Unfortunately a large part of this is lost in the urine but, if it is given in concentrated solution in quantities such as 15 g. per hour up to a total dose of 1 g. per kg. body weight and not exceeding 150 g. a week (Williams and Ryan, 1958) it may be possible to increase the serum albumin concentration sufficiently to produce a diuresis which is lasting in its effect on the œdema. Instead of albumin, dextran may be used in a sodium-free solution and again a diuresis can sometimes be produced.

Diuretics which deplete the body of sodium can sometimes help, the safest probably being chlorothiazide or hydrochlorothiazide. Organic mercurials are sometimes advocated, but they are best avoided. Sodium depletion can also be brought about by the use of katonium resin in doses of up to 45 g. a day. This is more effective and less difficult for the patient than almost complete removal of sodium from the diet (a very difficult thing to accomplish). Rosenheim and Spencer (1956) obtained very good results in a series of patients so treated. It was given on five days in each week and not on the remaining two. Biochemical estimations of sodium and potassium should be carried out fairly often at the beginning of this therapy although subsequently in cooperative patients monthly estimations have been found to be sufficient.

The rationale behind the various modes of therapy of the nephrotic syndrome has been reviewed by Talbot and his colleagues (1957), who conclude that the use of corticotrophin or corticosteroids occupies a unique position because these substances act to suppress the lesion primarily responsible for the development of the œdema.

References

Alwall, N. (1947): *Acta med. scand.*, **128**, 317.
Barr, J. S., and Chambers, J. W. (1958): *Scott. med. J.*, **3**, 123.
Beeson, P. B. (1956): *Yale J. Biol. Med.*, **28**, 81.
Birchall, R., and Alexander, J. E. (1950): *Medicine (Baltimore)*, 29, 1.
Borst, J. G. G. (1948): *Lancet*, **i**, 824.
Brod, J. (1956): *Ibid.*, **i**, 973.
Bull, G. M. (1955): *Ibid.*, **i**, 731, 777.

Bull, G. M., Joekes, A. M., and Lowe, K. G. (1949): *Lancet*, **ii,** 229.
Chambers, J. W., and Smith, G. (1957): *Brit. J. Surg.*, **45,** 160.
Charlton, D., Latner, A. L., Platt, J. W., Smart, G. A., Thompson, R. B., and Walker, W. (1958): *Acta med. scand.*, **161,** 33.
Debré, R., Royer, P. L., and Minor, Z. (1956): *Sem. Hôp. Paris*, **32,** 263.
De Navasquez, S. (1958): *Guy's Hosp. Rep.*, **107,** 399.
Doolan, P. D., Murphy, W. P., Wiggins, R. A., Carter, N. W., Cooper, W. C., Watten, R. H., and Alpen, E. L. (1959): *Amer. J. Med.*, **26,** 831.
Fairbrother, R. W. (1957): *The Practitioner*, **179,** 200.
Farquhar, M. G., Vernier, R. L., and Good, R. A. (1957): *J. exp. Med.*, **106,** 649.
Fishberg, A. M. (1955): *The Practitioner*, **175,** 408.
Gorrill, R. H. (1958): *Guy's Hosp. Rep.*, **107,** 405.
Guze, L. B., and Beeson, P. B. (1956): *New Engl. J. Med.*, **255,** 474.
Hart, E. L., and Magee, M. J. (1957): *Amer. J. Nursing*, **57,** 1323.
Iversen, P., and Brun, C. (1951): *Amer. J. Med.*, **11,** 324.
Jackson, G. G., Poirier, K. P., and Grieble, H. G. (1957): *Ann. intern. Med.*, **47,** 1165.
Kark, R. M., and Muehrcke, R. C. (1954): *Lancet*, **i,** 1047.
——, ——, Pirani, C. L., and Pollak, V. E. (1955): *Ann. intern. Med.*, **43,** 807.
Kass, E. H. (1955): *Amer. J. Med.*, **18,** 764.
Kolff, W. J. (1957): *Circulation*, **15,** 285.
——, and Berk, H. T. J. (1944): *Acta med. scand.*, **117,** 121.
Lange, K., Slobody, L., and Strang, R. (1953): *Proc. Soc. exp. Biol.* (*N.Y.*), **82,** 315.
MacDonald, R. A., Levitin, H., Mallory, G. K., and Kass, E. H. (1957): *New Engl. J. Med.*, **256,** 915.
McCracken, B. H., and Parsons, F. M. (1958): *Lancet*, **ii,** 885.
McGeown, M. G. (1956): *Brit. med. J.*, **ii,** 274.
Maxwell, M. H., Rockney, R. E., Kleeman, C. R., and Twiss, M. (1959): *J. Amer. med. Ass.*, **170,** 917.
Merrill, A. J., Wilson, J., and Timberlake, L. F. (1954): *Arch. intern. Med.*, **94,** 925.
Merrill, J. P. (1950): *Ann. intern. Med.*, **33,** 100.
Monzon, O. T., Ory, E. M., Dobson, H. L., Carter, E., and Yow, E. M. (1958): *New Engl. J. Med.*, **259,** 764.
Parsons, F. M., and McCracken, B. H. (1959): *Brit. med. J.*, **i,** 940.
Platt, R., and Davson, J. (1950): *Quart. J. Med.*, **19,** 33.
Pollak, V. E., Pirani, C. L., Muehrcke, R. C., and Kark, R. M. (1958): *Guy's Hosp. Rep.*, **107,** 353.
Raaschou, F. (1948): 'Studies of Chronic Pyelonephritis with Special Reference to the Kidney Functions', Copenhagen.
Rosenheim, M. L., and Spencer, A. G. (1956): *Lancet*, **ii,** 313.
Shaw, G. (1959): *Ibid.*, **i,** 15.
——, and Mair, J. (1954): *Ibid.*, **i,** 1031.
Skeggs, L. T. Jr., and Leonard, J. R. (1948): *Science*, **108,** 212.
Stansfeld, J. M., and Webb, J. K. G. (1954): *Brit. med. J.*, **i,** 616.
Talbot, N. B., Crawford, J. D., and Cook, C. D. (1957): *New Engl. J. Med.*, **256,** 1080.
Talbot, H. S. (1958): *J. Amer. med. Ass.*, **168,** 1595.
Taylor, W. H. (1959): *Lancet*, **ii,** 703.
Weiss, S., and Parker, F. Jr. (1939): *Medicine* (*Baltimore*), **18,** 221.
Williams, J. D. (1958): *Guy's Hosp. Rep.*, **107,** 373.
Williams, R. S., and Ryan, T. J. (1958): *Lancet*, **ii,** 988.

ADVANCES IN PSYCHOLOGICAL MEDICINE

By JACK R. EWALT, M.D.
Professor of Psychiatry, Harvard Medical School; Superintendent, Massachusetts Mental Health Center, Boston, Massachusetts

and LESTON L. HAVENS, M.D.
Instructor in Psychiatry, Harvard Medical School; Senior Physician, Massachusetts Mental Health Center, Boston, Massachusetts

Recent advances in psychiatric treatment have been rapid and extensive. The introduction of new methods of drug treatment, the application of psychoanalytical methods to the psychoses, the reorganization of mental hospital life in the interest of producing conditions favourable to psychological development and recovery, an increased emphasis on the treatment of other family members besides the patient, with the extension of treatment facilities to the community and home, are the chief of these advances. They have sprung from a growing current of experimental and clinical research on mental illness and health.

BIOCHEMICAL AND METABOLIC STUDIES

Perhaps the most spectacular change in American psychiatry in recent days has been the revival of interest in the chemical functioning of the nervous system and its relation to mental illness. Investigators have attempted to explain psychoses as the result of disturbed chemical regulation of synaptic transmission in the brain, basing their theories on a combination of studies involving experiments with lysergic acid and mono-amine oxidase inhibitors (Shore *et al.*, 1957; Koelle, 1958; Melander and Martens, 1958) and with abnormalities in adrenaline metabolism (Hoffer and Osmond, 1959; Rinkel and Solomon, 1957; Leach *et al.*, 1956). Serotonin is another metabolite of exceptional interest; knowledge of its central nervous system distribution is the accomplishment of workers such as Gaddum and his group in Scotland (Amin *et al.*, 1954).

In addition to studies of brain chemistry, studies on general metabolism have continued. These have included investigations of carbohydrate metabolism (Henneman *et al.*, 1954) and of phosphate excretion (Stevenson *et al.*, 1957). Evidence of unidentified aromatic substances in the urine of schizophrenics has been reported (McGeer *et al.*, 1957) and other workers have related disturbances of psychological state to changes in the excretion patterns of adrenaline and arterenol (Funkenstein, 1956; Elmadjian *et al.*, 1957).

DRUG THERAPY

This interest in the chemistry of behaviour has had striking results in the therapeutic field. Successful drug treatment of mental illness has been a

goal of many years' standing, but the past waves of enthusiasm for the barbiturates, bromides, insulin and other therapeutic drugs do not match the degree of hope and enthusiasm engendered by clinical experience with the newer sedatives or tranquillizers. The first of these, chlorpromazine and reserpine, introduced respectively from France and India, have been joined by an increasing host of other compounds. Their use in mental hospital practice has reduced the need for insulin coma and electroconvulsive treatment, improved the atmosphere of ward life and assisted many patients to rejoin the community. They appear to have been most successful with schizophrenic patients and only recently have clinical trials of the new anti-depressant medications been undertaken. Follow-up studies on the results of prolonged therapeutic use of tranquillizers have begun to appear (Winkelman, 1957).

The mode of action of such materials as chlorpromazine and reserpine has not yet been fully determined. Certainly there is some agreement that, in contrast, for example, to the barbiturates, they permit a high degree of sedation with relatively little hypnotic effect. Attempts to explain the specific functions of these agents in the treatment of psychoses have included studies of their actions on brain electrical potentials, catechol amine storage and lysergic acid and serotonin effects (Garattini and Valzelli, 1958; Muscholl and Vogt, 1957; Shore *et al.*, 1955). These and other actions of tranquillizers have led Woolley and the group at the Rockefeller Institute to revive interest in additional chemicals known to influence patients with psychoses. Woolley (1958), for example, has studied the tranquillizing and antiserotonin activity of nicotinamide.

These attempts at a chemical understanding of psychoses have paralleled a revival of interest in brain physiology, particularly as it relates to human behaviour. Magoun and his associates have stimulated a great deal of research in this area by their formulations of the concept of the brain reticular formation. Their investigations and those of others have recently been summarized in the publication of a symposium at the Henry Ford Hospital in Detroit (Jasper *et al.*, 1958). These studies are of special clinical interest because of the effects produced on the brain reticular formation by certain tranquillizing drugs (Rinaldi and Himwich, 1957).

In addition, work in the conditioning laboratories at Harvard by Skinner, Lindsley and their associates, has established correlations between specific neurophysiological states and patterns of human behaviour. Dews (1956) and others have used these conditioning techniques to investigate the behavioural effects of drugs, notably stimulants, barbiturates and tranquillizers. Such studies have brought behaviour nearer to observation on a scientific basis.

The use of convulsive therapy is on a sharp decline in the United States. Drug treatment has largely replaced the therapeutic use of insulin coma in schizophrenia and chemical anti-depressants are already making inroads on the popularity of electric convulsive treatment. The use of the short-

acting muscle relaxant, suxamethonium chloride, to modify electrically induced seizures, has spread widely. Controlled studies, comparing electroconvulsive treatments with and without muscle relaxants, have shown no significant differences in the treatment results (Havens, 1958).

PSYCHOANALYTICAL THERAPY

The psychoanalytical studies of the psychoses, initiated by Freud, Abraham and Jung, and carried forward by other European clinicians, were at first mainly concerned with understanding symptoms and with the construction of theory. Abraham, for example, when he did pioneer work on manic-depressive psychoses early in the century, laid emphasis on the developmental fixations and their clinical representations. In contrast, recent studies of this same group of disorders have emphasized the possible etiological importance of specific family attitudes and relationships common in the early life of such patients and the treatment procedures best suited for the resulting disorder (Cohen *et al.*, 1954). The specific problems of treating schizophrenic patients with analytical methods have also been subject to study, and the need of interpreting in a new light phenomena familiar from the therapy of neurotic patients has been underscored (Hendrick, 1958).

The investigation of the psychoses has led to work with these patients in group therapy (Hora, 1958) and to the delineation of the particular methods appropriate for group therapy with psychotic people (Standish *et al.*, 1952). In addition, psychoanalytical studies of the psychoses have been widely extended to work with children and one of the most interesting of these studies has resulted in Rochlin's (1959) proposal of the term 'loss complex' for 'depression', because of specific differences in the clinical syndromes and underlying dynamics presented by children.

MULTI-DISCIPLINARY STUDIES

The increasing interest of the experimental psychologist in the phenomena of psychiatry has brought to the clinical field a concern with quantitative and statistical techniques from the lack of which it had long suffered. Abnormalities of perception, the development of cognition and the results of sensory deprivation are some of the recently studied subjects of special interest to psychological medicine. Many such researches involve the application of methods from different disciplines, and the first efforts have already been made to bring sociology, psychology and physiology simultaneously to bear on common problems. Work on sensory deprivation is perhaps of special interest and typical of the investigations in this area. The first observations of Hebb on sensory deprivation and sensory patterning have led to a large volume of research. Careful social, psychological and physiological studies have been carried on at the National Institutes of Health and elsewhere, and the work has recently been summarized in the publication of a symposium in Boston (Solomon, awaiting publication.)

Other multi-disciplinary studies include Fox's (Fox *et al.*, 1958) attempts to correlate physiological and psychological changes in subjects of both normal and pathological types under varying degrees of stress. The effects of tranquillizing drugs have been similarly investigated and the concept advanced that these drugs affect people according to their individual personality patterns (Klerman *et al.*, 1959). The use of the polygraph, permitting simultaneous recording of several physiological parameters, has made possible study and comparison of both doctor and patient during psychotherapy (DiMascio *et al.*, 1957). The problem of dream formation has also inspired efforts to relate psychological and physiological phenomena (Ullman, 1958).

'MILIEU THERAPY'

The use of the hospital environment as an instrument for the treatment of mental illness (what has come to be called 'milieu therapy') is a development pioneered in Great Britain and taken up in Canada and the United States. Generally there has been an attempt to improve the living conditions of hospitalized mental patients and to organize institutional procedures in a way that preserves the patients' dignity and self-respect. The 'open' hospital (in which few if any wards are locked), the encouragement of voluntary rather than certified admissions, the assumption by patients of some responsibility for their own behaviour and organization (as through a system of 'Patient Government'), and the reduction in the use of restraint and seclusion are all steps in the same direction. Some hospital organizations, such as that of Maxwell Jones in England, have been specifically designed for the needs of one type of patient (Jones, 1953). Other institutions have evolved 'milieux' for a variety of patient types and have emphasized the value of such milieu therapy for the resocialization and remotivation of psychotic patients.

The development of milieu therapy in the United States is well represented by the work of Stanton and Schwartz (1954). These observers have highlighted the influence of staff attitudes and disagreements on patients' behaviour and have brought psychoanalytical insight to bear on administrative issues. Recent experience in the field was summarized at a symposium in Boston (Greenblatt, 1957). Studies of individual hospitals have also been completed and published (Belknap, 1956; Caudill, 1958).

While mental hospitals have set the goal of being themselves therapeutically helpful communities, there has arisen between the hospital and the outside community a number of institutions to smooth the patient's transition from one to the other. 'Half-way houses', in which patients may continue to find some of the support they experienced in the hospital, are way-stations in the patient's movement toward fuller community responsibility. Day hospitals, developed by Cameron at McGill, provide day-time treatment and social facilities for patients able to sleep at home. Night hospitals make possible a continuance or early resumption of work

or schooling while providing the patient with a home at night. These developments have in common the goal of reducing the mental hospital's (and the mental hospital patient's) isolation from the community. Still another agency, the psychiatric emergency service, first developed in Holland by Querido, has furthered this ideal. Psychiatric emergency services, usually underwritten by civic governments, have made available teams of doctors, nurses and social workers ready to visit disturbed patients in their homes and to prevent the development of illnesses demanding hospitalization. There has grown up an interest in family diagnosis and treatment, the delineation and therapy of those domestic interpersonal stresses that may lie behind the patient's symptoms.

Perhaps the most detailed studies on the role of conflict within the family are those of John Spiegel and Florence Kluckhohn at Harvard (Spiegel, 1957). The vast literature on the family has recently been summarized, together with his own researches, by Ackerman (1958). Lidz has given special attention to the family patterns of schizophrenic patients (Lidz *et al.*, 1957).

A still wider concern for the conditions behind individual psychiatric illness has prompted the development of psychiatric epidemiology. Beginning in Denmark and Sweden, social and familial studies of mental illnesses have determined the social conditions and genealogy of certain illnesses, the incidence of many symptoms in the general population and the extent to which mental illnesses and the types of treatment are a function of economic and social class (Hollingshead and Redlich, 1958; Opler, 1956).

Both in Canada and in the United States (through the Joint Commission on Mental Illness and Health) large-scale assessments of mental health resources have been made possible by government grants. Such studies have clarified the economic impact of mental illness, the goals of mental health programmes and the presently available treatment resources. Each study will have findings and recommendations for a national health programme, with the aim of furthering present use and future development of mental health resources. The World Health Organization has also made possible studies of mental health facilities, in widely separated parts of the globe, and to highlight the importance of this work and to attract support to it, 1960 is to be World Mental Health Year.

CONCLUSION

These brief statements indicate that psychiatry is in a period of great change. The movement is away from dogmatic and inclusive orderings of the whole field and towards an experimental and therapeutic orientation. This is but one phase of psychiatry's larger scientific growth, in which it follows medicine, from the demonic and mystical to the pragmatic and empirical. Such developments will throw medicine and psychiatry closer and closer together, in the common achievement of a fuller human biology and psychology.

References

Ackerman, N. (1958): 'The Psychodynamics of Family Life', New York.

Amin, A. H., Crawford, T. B. B., and Gaddum, J. H. (1954): *J. Physiol. (Lond.)*, **126,** 596.

Belknap, I. (1956): 'Human Problems of a State Mental Hospital', New York.

Caudill, W. A. (1958): 'The Psychiatric Hospital as a Small Society', Cambridge, Mass.

Cohen, M. B., Baker, G., Cohen, R. A., Fromm-Reichmann, F., and Weigert, E. V. (1954): *Psychiatry*, **17,** 103.

Dews, P. B. (1956): *Ann. N.Y. Acad. Sci.*, **65,** 268.

DiMascio, A., Boyd, R., and Greenblatt, M. (1957): *Psychosom. Med.*, **19,** 99.

Elmadjian, F., Hope, J. M., and Freeman, H. (1957): *A.M.A. Arch. Neurol. Psychiat.*, **77,** 399.

Fox, H. M., Murawski, B. J., Thorn, G. W., and Gray, S. (1958): *A.M.A. Arch. intern. Med.*, **101,** 859.

Funkenstein, D. H. (1956): *J. nerv. ment. Dis.*, **124,** 58.

Garattini, S., and Valzelli, L. (1958): *Science*, **128,** 1278.

Greenblatt, M. (1957): 'The Patient and the Mental Hospital', Glencoe, Ill.

Havens, L. L. (1958): *Dis. nerv. Syst.*, **19,** 29.

Hendrick, I. (1958): *J. Amer. psychoanal. Ass.*, **6,** 672.

Henneman, D. H., Altschule, M. D., and Gonez, R. M. (1954): *A.M.A. Arch. intern. Med.*, **94,** 402.

Hoffer, A., and Osmond, H. (1959): *J. nerv. ment. Dis.*, **128,** 18.

Hollingshead, A. D., and Redlich, F. C. (1958): 'Social Class and Mental Disorder: A Community Study', New York.

Hora, T. (1958): *J. Hillside Hosp.*, **7,** 110.

Jasper, H., Proctor, L., Knighton, R., Noshay, W., and Costello, R. (1958): 'Reticular Formation of the Brain', Henry Ford Hospital International Symposium, Boston, Mass.

Jones, Maxwell (1953): 'The Therapeutic Community', New York.

Klerman, G., DiMascio, A., Greenblatt, M., and Rinkel, M. (1959): In 'Biological Psychiatry', edited by J. H. Masserman, New York, vol. 1, p. 224.

Koelle, G. B. (1958): *J. clin. exper. Psychopath.*, **19,** 37.

Leach, M. E., Cohen, M., Heath, R. G., and Martens, S. (1956): *A.M.A. Arch. Neurol. Psychiat.*, **76,** 635.

Lidz, T., Cornelison, A. R., Fleck, S., and Terry, D. (1957): *Psychiatry*, **20,** 329.

McGeer, P. L., McNair, F. E., McGeer, E. G., and Gibson, W. C. (1957): *J. nerv. ment. Dis.*, **125,** 166.

Marrazzi, A.: Personal communication.

Melander, B., and Martens, S. (1958): *Dis. nerv. Syst.*, **19,** 478.

Muscholl, E., and Vogt, M. (1957): *J. Physiol. (Lond.)*, **136,** 7P.

Opler, M. K. (1956): 'Cultural Society and Human Values', Springfield, Ill.

Rinaldi, F., and Himwich, H. E. (1957): *Ann. N.Y. Acad. Sci.*, **61,** 27.

Rinkel, M., and Solomon, H. C. (1957): *J. clin. exper. Psychopath.*, **18,** 323.

Rochlin, G. (1959): *J. Amer. psychoanal. Ass.*, **7,** 299.

Shore, P. A., Mead, R. G., Kuntzman, S. S., and Brodie, B. B. (1957): *Science*, **126,** 1063.

——, Silver, S. L., and Brodie, B. B. (1955): *Ibid.*, **122,** 284.

Solomon, P.: 'Symposium on Sensory Deprivation'. In the press.

Spiegel, J. P. (1957): In 'The Patient and the Mental Hospital', edited by M. Greenblatt, Glencoe, Ill., chap. 32.

Standish, C. T., Gurri, J., Semrad, E. V., and Day, M. (1952): *Amer. J. Psychiat.*, **109,** 283.

Stanton, A. H., and Schwartz, M. S. (1954): 'The Mental Hospital', New York.

Stevenson, J. A. F., Derrick, J. B., Hobbs, G. E., and Metcalfe, E. V. (1957): *A.M.A. Arch. Neurol. Psychiat.*, **78,** 312.

Ullman, M. (1958): *J. clin. exp. Psychopath.*, **19,** 128.

Winkelman, N. W., Jr. (1957): *Amer. J. Psychiat.*, **113,** 961.

Woolley, D. W. (1958): *Science*, **128,** 1277.

ADVANCES IN ALLERGY

By PAUL KALLÓS, M.D., F.A.C.A.(Hon.)
From the Margareta and Erik Wihlborg Laboratory for Research in Allergy, Hälsingborg, Sweden

A BRIEF review of the therapeutic advances in this ever-changing and growing field must be limited to the management of the allergic disorders *sensu strictiori:* i.e. seasonal and perennial allergic rhinitis, bronchial asthma, urticaria and angioneurotic œdema, infantile eczema and Besnier's prurigo and contact eczema.

DESENSITIZATION

In 1953, in his excellent review of the role of specific desensitization in the treatment of allergic conditions, Harley stated that 'despite all the recent advances in the knowledge of allergy, it is true to say that, apart from the relatively small percentage of cases in which avoidance of contact with the specific allergen is a therapeutic practicability, desensitization still constitutes the main and most satisfactory armament in the treatment of recurrent and chronic allergic diseases'. This is still entirely true. The method of desensitization, which was outlined by Noon in 1911 and, after his untimely death, developed by Freeman, consists of the subcutaneous administration of 'a graded series of doses of a protein extract of the specific allergen to which the patient is sensitive' (Harley, 1953).

What is required now is (a) a better understanding of the chemistry of the allergenic fractions of different natural products and (b) reliable *in vitro* methods for the exact standardization of extracts. Promising work in this field is in progress in many laboratories. Important results concerning the chemical nature of grass pollen allergens and the standardization of pollen extracts have been achieved by Augustin (1958, 1959), Johnson and Thorne (1958), Britton *et al.* (1958), and Feinberg (1958). Stanworth (1958) has succeeded in preparing pure allergenic fractions from crude horse dandruff extracts. It is to be hoped that further basic research along these lines will soon improve the quality of allergenic extracts and enhance their therapeutic (and diagnostic) value.

PENICILLINASE

An entirely new form of causal therapy of certain allergic manifestations has been devised by Becker (1956, 1958, 1959). This consists of the treatment of allergic reactions to penicillin with a specific enzyme, penicillinase. Penicillinase hydrolyses penicillin by opening the β-lactam ring of the penicillin molecule to penicilloic acid. This latter compound lacks antibiotic activity and allergenicity and Becker (1956) showed that intramuscularly administered penicillinase inactivates circulating penicillin in healthy adults and guinea-pigs without having any toxic or allergenic effects. His assumption was that 'if in treating an antigen-antibody reaction one is able to interfere with the reaction by inactivating the antigen with an enzyme,

then that treatment can be expected to be sound and effective'. His results in 46 patients with various allergic reactions to penicillin bear this out. Penicillinase was given in a dosage of 800,000 to 1,600,000 units intramuscularly or intravenously. (One unit of penicillinase is the amount inactivating one unit of penicillin per minute at 25° C., pH 7, *in vitro*.)

Twenty-four of these patients, who were suffering from urticaria, angioneurotic œdema or exfoliative dermatitis, with or without joint involvement, were treated with intramuscular penicillinase alone, with uniformly good results. The signs and symptoms of the allergic disorder caused by penicillin subsided only a few hours after the administration of penicillinase. In 22 cases with similar syndromes steroid hormones and/or antihistamines were given either before or simultaneously with the penicillinase treatment. According to Becker (1958), 'in 20 of these patients the favourable clinical response seemed to be directly attributable to the penicillinase'. He states that only a few patients complained of pain at the site of the penicillinase injection. 'No systemic toxic reactions to single or multiple injections of penicillinase were noted'.

These results were corroborated by Minot and Davis (1957), Zimmerman (1958) and Unger and Nemuth (1958). Although penicillinase should be administered as soon as possible after the onset of the allergic manifestations, it is of interest to note that in a number of cases 'dramatic' results were obtained in spite of the fact that penicillinase was given some weeks or months after the onset of the allergic syndrome. It is well documented that in a number of cases (including urticaria, angioneurotic œdema, painful swelling of joints, dermatitis exfoliativa, hæmorrhagic lesions and one case of renal insufficiency with oliguria of three days' duration) the administration of penicillinase some weeks or months after the onset of the allergic syndrome cleared lesions which were resistant to other forms of therapy within twenty-four hours and the patients recovered. In other cases with severe vascular damage, penicillinase was less efficacious or ineffective. Becker (1958) assumes that the allergic vasculitis may have become 'self perpetuating' and thus continued after the destruction of the allergen.

In contrast to the findings of Becker and of Chen, Bard and Belsito (1958), penicillinase is allergenic in guinea-pigs and rabbits (Fisher *et al.*, 1957) and in man as well (Weiss and Crepea, 1959). This was to be expected. Penicillinase is a bacterial protein with a molecular weight of 50,000. The purified preparation available is extracted from cultures of *B. cereus*. Reports of severe reactions after therapy with penicillinase have been published recently by Johnston and Cazort (1959), Hyman (1959) and Reisch (1959). These were most probably caused by allergy to penicillinase.

In the clinical literature concerning the therapeutic use of penicillinase it is often stated that this enzyme has been successfully used in 'delayed' reactions to penicillin. This is most inaccurate. All the cases described in the literature suffered from allergic syndromes of the *immediate type*. Reactions of the delayed type (Kallós and Kallós-Deffner, 1956; Kallós, 1956) have not been treated with penicillinase hitherto. A long-lasting reaction of the immediate (evanescent) type, such as urticaria or serum-sickness, should not be called 'delayed'. It is well known that there are fundamental differences between the immediate and delayed types of allergic reactivity (Kallós, 1954, 1958), and these terms should not be used in another sense.

The most dangerous allergic reaction to penicillin is acute shock within a very few minutes after administration. In such cases the shock must be

controlled with adrenaline, antihistaminics and steroid hormones before administering penicillinase.

In spite of its shortcomings penicillinase is obviously a most useful new therapeutic agent. Furthermore, as Becker (1958) states, 'it is hoped that this study will stimulate the search for other enzymes specific for antigens responsible for the many allergic diseases with which humanity is plagued'.

SYMPTOMATIC TREATMENT

Patients with probably allergic syndromes consult the general practitioner either when they have an acute attack or about long-lasting symptoms, such as chronic urticaria, eczema and asthma. In the latter group secondary changes, such as emphysema and/or chronic bronchitis in asthmatics, and lichenification in eczematous patients, are often prevalent. Sometimes the cause is obvious, as in cases of seasonal rhinitis and asthma (pollinosis), drug allergy and allergic occupational diseases, such as contact eczema, but in the majority of cases the cause eludes direct recognition and the patient has to be referred to an allergist. In all cases, however, symptomatic treatment is necessary. Rational symptomatic treatment is one of the backbones of allergy therapy. Some aspects of symptomatic treatment have been expertly reviewed in *The Practitioner*: the use of antihistaminic drugs by Frankland (1953), and that of corticotrophin, cortisone and hydrocortisone by Williams (1955). Their conclusions are still valid.

From the practical point of view it seems rational to differentiate between non-specific and specific symptomatic treatment. Non-specific therapeutic measures influence the reactivity of the organism as a whole and can thereby secure symptomatic relief. Specific symptomatic treatment is aimed at either improving or terminating certain symptoms, such as bronchospasm or itching, or directed against the effect of certain mediators released from damaged cells in connexion with the allergic reaction, such as histamine.

NON-SPECIFIC SYMPTOMATIC TREATMENT

Williams (1955) stated that 'hormonal therapy has been shown to be the major advance in treatment' of the allergic diseases. His excellent review covers the use of corticotrophin, cortisone and hydrocortisone. Since then new corticosteroid derivatives have been introduced and greater clarity has been obtained concerning the merits and disadvantages of this form of therapy. Corticotrophin (given intramuscularly or intravenously), cortisone and hydrocortisone (administered orally or topically) suppress the symptoms of allergic diseases in about 80 per cent. of cases, even if these are very severe and otherwise intractable. Corticotrophin exerts its effect by stimulating the adrenal cortex to secrete hydrocortisone, cortisone and, to a lesser extent, also aldosterone and corticosterone. The newer corticosteroid derivatives have diminished the use of corticotrophin in general practice.

The treatment of allergic, rheumatic and other 'collagen' diseases with cortisone or hydrocortisone is not substitution therapy. There is no adreno-

cortical insufficiency in such cases (Dougherty, 1954; Ingle and Burton, 1953; Kallós, 1952, 1954, 1958; Siegel *et al.*, 1956). The amounts needed for the treatment of such diseases are 'unphysiological': i.e. they exceed the amount secreted by the normal adrenal cortex and necessary for maintaining the normal functional state of the organism (homeostasis). Consequently, systemic administration causes not only the desired 'anti-inflammatory' effect, the mechanism of which is not entirely understood, but also profound metabolic, endocrine, neuromuscular, immunological and cytological effects (Engel, 1954; Ingle and Burton, 1953; Williams, 1955).

These include: increase of gluconeogenesis; lowered renal threshold for glucose; increased resistance to insulin; increased absorption and storage of fat; increased protein catabolism and/or decreased anabolism; sodium and water retention, loss of potassium and chloride; mobilization of calcium from the skeleton (osteoporosis); hypercortisonism (Cushing's syndrome); retardment of growth in children on long-term therapy; suppression of corticotrophin and hydrocortisone secretion; changes in the muscular tone and functional capacity of the musculature; exaggerated sense of well-being, and in single cases (probably predisposed individuals) serious, though transitory, psychotic reactions, such as severe depression; suppression of signs and symptoms of infectious states and inhibition of the normal defence mechanisms (such as inflammatory reactions), which can give rise to overwhelming infections (tuberculosis, sepsis); functional and morphological involution of the lymphoid and reticulo-endothelial system; peripheral eosinopenia; retarded wound-healing; increased gastric secretion and more or less sudden appearance of gastric or duodenal ulceration.

These consequences of systemic cortisone administration must always be borne in mind when steroid therapy is attempted or used.

A great number of synthetic derivatives of 11, 17 oxysteroids has been developed in the attempt to 'dissociate' the 'anti-inflammatory' (i.e. therapeutic) and hormonal effects (so called side-effects). In rapid succession preparations were introduced which, milligram by milligram, possess considerably greater anti-inflammatory effect than cortisone and hydrocortisone and have less side-effects, especially as regards mineral metabolism (sodium and water retention, potassium depletion). Dehydrogenation of cortisone at positions 1 and 2 gave ***prednisone*** and the similar analogue of hydrocortisone was introduced as ***prednisolone***. The anti-inflammatory effect of these preparations is about four times that of hydrocortisone. The usual single oral therapeutic dose of 20 mg. of hydrocortisone could be substituted by 5 mg. of either of these preparations with no lag period or exacerbation of the disease. The 'side-effects' are principally the same but less pronounced.

The next step was the introduction of *triamcinolone* and of methylprednisolone: 4 mg. of these derivatives has the same therapeutic effect as 5 mg. of prednisone or prednisolone. The side-effects are far less pronounced but certainly not absent (Hart, 1958; Wells, 1958). These preparations are widely used in the therapy of allergic disorders. The latest preparation to be marketed is *dexamethasone*, 0.5 mg. of which has the same therapeutic effect as 4 mg. of triamcinolone. Dexamethasone is extremely useful in the therapy of severe asthma and other severe allergic diseases, such as hay fever,

urticaria and angioneurotic œdema. A daily dose of 1.5 to 3 mg. usually suppresses the acute symptoms very quickly and then a maintenance dose of 0.5 to 1 mg. is sufficient. The mineralo-corticoid effects are modest but not absent (Boland, 1958; Bunim *et al.*, 1958; Gertaud, 1959; Neustadt, 1959; Slater *et al.*, 1959). The far more serious side-effects—the risk of peptic ulceration and overwhelming infections—are unchanged. Occasionally some other unexplained 'side-effects' may also occur. Wells (1958) for instance, observed in a number of cases treated with triamcinolone signs and symptoms resembling acute rheumatoid arthritis. The arthritis disappeared as soon as prednisolone was given instead of triamcinolone. Dyspepsia and profound musculatory weakness are not uncommon in patients treated with higher doses of triamcinolone. In the course of long-term steroid therapy diffuse mesenchymal reactions can develop, which resemble the lesions seen in systemic lupus erythematosus and/or polyarteritis nodosa. Such changes were first observed in animal experiments by Pagel and myself (Kallós, 1952, 1954, 1958) and by Dougherty (1954) and later on in clinical cases by Slocumb and his co-workers (1957).

Nevertheless, the introduction of the delta-steroids (prednisone, prednisolone) triamcinolone and dexamethasone is a definite advance and a splendid achievement. Treatment with these preparations of allergic disorders, especially of serious but self-limited allergic manifestations, such as drug allergies and status asthmaticus, but also long-term treatment in otherwise intractable asthmatics, is much safer and the results are more reliable. On the other hand, they must be used with discrimination. As Ward (1959) has pointed out: 'Generally, the best steroid for treatment . . . today is that which is administered by the physician who selects his patient properly, supplements steroid therapy with other appropriate measures of treatment, supervises the administration carefully, and regulates the dosage to achieve a reasonable . . . effect with avoidance of, or a minimum of, undesired effects'.

The corticosteroids exert their 'anti-inflammatory' action at the cellular level. Systemic administration always involves some risk of complications. For these reasons topical administration must be preferred whenever possible. Infantile eczema, Besnier's prurigo and contact dermatitis react quite uniformly in a favourable way to treatment with 1 per cent. hydrocortisone ointment or liniment. There is as yet no convincing evidence that higher concentrations (2.5 per cent.) or the newer steroids are more effective. Williams (1955) and Stoughton (1959) have reviewed this form of treatment very adequately. A word of warning is necessary about combinations of hydrocortisone, or other steroids, with antibiotics in ointments. From the point of view of the allergist such combinations are definitely undesirable. Antibiotics are powerful sensitizing agents. Hexachlorophane is preferable. In my experience 'vioform' is an excellent antibacterial and antifungal agent for dermatological use, especially as it also has an anti-eczematous action.

Ophthalmic solutions of hydrocortisone (0.5 to 2.5 per cent.) are widely used in the treatment of allergic eye diseases, particularly conjunctivitis, some forms of

keratitis and kerato-conjunctivitis in allergic individuals, scleritis and uveitis. This, however, is a field which should be reserved for the ophthalmologist (Theodore and Schlossman, 1958).

SPECIFIC SYMPTOMATIC TREATMENT

This field of therapy is dominated by two groups of drugs: sympathomimetic (adrenergic) agents and antihistamines.

It is well known that *adrenaline* in small doses (0.5 mg. subcutaneously) gives quick but temporary relief from distressing allergic symptoms, such as asthma, rhinitis, conjunctivitis, urticaria or angioneurotic œdema. In all these, dilatation of vessels and/or spasm of smooth musculature causes the symptoms. Ephedrine and its derivatives have a longer-lasting effect and can be given orally. Soluble theophylline derivatives given intravenously or in the form of rectal suppositories (0.2 to 0.5 g.) have an excellent anti-asthmatic effect (Kallós and Kallós-Deffner, 1957).

The introduction of a device called '*medihaler*' is—in my opinion—a definite advance in the symptomatic treatment of asthma.

The 'medihaler' consists of a light metal bottle containing micronized particles of the active drug—adrenaline or isoprenaline—in the range of optimum therapeutic particle-size to ensure full alveolar absorption. The particles are suspended in an inert and non-toxic vehicle, a mixture of 'freons'. The bottle is closed with a special measuring valve. The boiling-point of the freon-mixture lies below normal room temperature. At room temperature the mixture boils and the pressure rises until its steam pressure is reached. Consequently, when the valve is opened the compressed gas expands rapidly and parts of the contents of the container are expelled as a true aerosol. At the same time, the pressure in the bottle is reduced; but this reduction is immediately compensated by the transformation into gas of an equivalent part of the remaining freon-mixture. When the measuring valve is opened a uniform amount of aerosol is delivered, containing 0.15 mg. of adrenaline-bitartrate or 0.06 mg. of isoprenaline sulphate, and can be inhaled through a special mouth-piece.

In an extensive controlled study we have shown (Kallós and Kallós-Deffner, 1959) that the inhalation of isoprenaline aerosol is extremely effective in asthmatic attacks, in attacks of dry, non-productive cough and as a prophylactic measure in chronic asthmatics in an attempt to prevent dyspnœa on exertion. Satisfactory improvement of the respiratory values and the subjective state occurred uniformly after the inhalation of only 0.24 mg. of isoprenaline sulphate—a remarkably low dose. The side-effects, chiefly tachycardia, are negligible. The 'medihaler' principle can probably be used for other drugs, too, and further progress in the field of inhalational therapy can be expected.

The role of *antihistaminic agents* in the therapy of allergic disorders has been evaluated in *The Practitioner* by Frankland (1953). Since then some new and more powerful compounds, such as the phenothiazine derivatives (chlorpromazine, promethazine and diethazine) and thenalidine, have been introduced. Powerful antihistaminics also have sedative effects. It is therefore often necessary to combine them with a suitable central nervous stimulant. Such a combination, consisting of tripelennamine and methylphenidate hydrochloride, is very useful in cases of hay fever and urticaria. Cerletti and Rothlin (1955) introduced a combination of an ionizable

calcium salt and thenalidine and showed that calcium and the antihistamine interact in a favourable way, thus mutually increasing their effectivity and tolerability.

CONCLUSION

There is more, however, to the treatment of allergic disorders than the skilful administration of allergens and drugs. Rational treatment aims not only at terminating the signs and symptoms of the disease, but also at curing the patient, and in this wider aim helpful understanding can often be more effective than drugs.

References

Augustin, R. (1958): *Int. Arch. Allergy*, **11**, 153.
—— (1959): *Immunology*, **2**, 1, 148.
Becker, R. M. (1956): *New Engl. J. Med.*, **254**, 952.
—— (1958): *Ann. intern. Med.*, **48**, 1228.
—— (1959): *J. Amer. med. Ass.*, **169**, 1148.
Boland, E. W. (1958): *Calif. Med.*, **88**, 417.
Britton, C. J. C., *et al.* (1958): *Int. Arch. Allergy.*, **13**, 305.
Bunim, J. J., *et al.* (1958): *Arthr. Rheumat.*, **1**, 313.
Cerletti, A., and Rothlin, E. (1955): *Int. Arch. Allergy*, **6**, 230.
Chen, J. Y. P., Bard, J. W., and Belsito, A. A. (1958): *Antibiot. Ann.*, **5**, 321.
Dougherty, Th. F. (1954): *Progr. Allergy*, **4**, 319.
Engel, F. L. (1954): *Ibid.*, **4**, 227.
Feinberg, J. G. (1958): *Int. Arch. Allergy*, **11**, 129.
Fisher, J. P., *et al.* (1957): *J. Allergy*, **28**, 423.
Frankland, A. W. (1953): *The Practitioner*, **170**, 355.
Freeman, J. (1950): 'Hay Fever, A Key to the Allergic Disorders', London.
Gertaud, P. (1959): *Sem. Hôp. Paris*, **35**, 367.
Harley, D. (1953): *The Practitioner*, **170**, 338.
Hart, D. F. (1958): *Lancet*, **ii**, 495.
Hyman, A. L. (1959): *J. Amer. med. Ass.*, **169**, 593.
Ingle, D. J., and Burton, L. B. (1953): 'Physiological and Therapeutic Effect of Corticotrophin (ACTH) and Cortisone', Springfield, Ill.
Johnson, T., and Thorne, H. V. (1958): *Int. Arch. Allergy*, **13**, 257, 276, 291.
Johnston, T. G., and Cazort, A. G. (1959): *J. Amer. med. Ass.*, **169**, 23.
Kallós, P. (1952): *Progr. Allergy*, **3**, 1.
—— (1954): *Ibid.*, **4**, 1.
—— (1956): *J. Amer. med. Ass.*, **161**, 900.
—— (1958): *Progr. Allergy*, **5**, IX.
——, and Kallós-Deffner, L. (1956): *Antibiot. et Chemother.* (*Basel*), **3**, 145.
——, —— (1957): *Int. Arch. Allergy*, **10**, 129.
——, —— (1959): *Ibid.*, in the press.
Minot, A. M., and Davis, G. M. (1957): *J. Amer. med. Ass.*, **165**, 222.
Neustadt, D. H. (1959): *Ibid.*, **170**, 1253.
Reisch, M. (1959): *J. Amer. med. Ass.*, **169**, 594.
Siegel, S. C., *et al.* (1956): *J. Allergy*, **27**, 504.
Slater, J. D. H., *et al.* (1959): *Lancet*, **i**, 173.
Slocumb, Ch. H., *et al.* (1957): *Ann. intern. Med.*, **46**, 86.
Stanworth, D. R. (1958): *Int. Arch. Allergy*, **11**, 170.
Stoughton, R. B. (1959): *J. Amer. med. Ass.*, **170**, 1311.
Theodore, F. H., and Schlossman, A. (1958): 'Ocular Allergy', Baltimore.
Unger, A. M., and Nemuth, H. I. (1958): *J. Amer. med. Ass.*, **167**, 1237.
Ward, L. E. (1959): *Ibid.*, **170**, 1318.
Weiss, R. C., and Crepea, S. D. (1959): *J. Allergy*, **30**, 337.
Wells, R. (1958): *Lancet*, **ii**, 498.
Williams, D. A. (1955): *The Practitioner*, **175**, 435.
Zimmerman, M. C. (1958): *Antibiot. Ann.*, **5**, 312.

ADVANCES IN THE TREATMENT OF ARTHRITIS AND CHRONIC RHEUMATISM

By S. J. HARTFALL, T.D., M.D., B.Sc., F.R.C.P.

Professor of Clinical Medicine, University of Leeds; Physician, General Infirmary, Leeds, and the Royal Bath Hospital, Harrogate

WHEN the subject of arthritis and chronic rheumatism was last reviewed in 'Advances in Treatment' (Bauer and Ropes, 1956), the comment was made that factors influencing the course of these diseases for better or worse were only beginning to be appreciated, and that true curative therapy is certainly not at hand. In the interval it cannot be said that any fundamental contribution to treatment has been made; yet perhaps the time has come again to take stock of the small advances recorded in the field of therapy.

It is nearly ten years since the dramatic effect of cortisone on rheumatoid arthritis was first described and it is perhaps natural that in the period under review much attention has been given to the newer anti-inflammatory steroids. This, despite the findings of the Medical Research Council and Nuffield Foundation Joint Committee on 'Long-term results in early cases of rheumatoid arthritis treated with either cortisone or aspirin' (1957a). The view there expressed was that there appeared to be no significant advantage in employing cortisone therapy; yet much investigation and many clinical trials have been published in an endeavour to assess the value of steroid derivatives in the rheumatic diseases. (In parenthesis, it is to be noted that the use of aspirin itself has not escaped criticism.) Thus, clinicians in the rheumatic field have collected much evidence of the value and dangers of the newer steroids, such unwanted side-reactions as the increased incidence of gastro-duodenal ulcer and its complications when the first Δ^1 (predni-) steroids were used (Black *et al.*, 1957; M.R.C. and Nuffield Foundation Joint Committee, 1957b). The modification of some old and the occurrence of some new adverse hormonal effects have been noted with the more powerful recently developed preparations—triamcinolone, dexamethasone and methylprednisolone. The advent of each of these was characterized by new hopes for a perfect anti-inflammatory agent. This has still to be attained. The value and hazards of local intra-articular hydrocortisone and related preparations have also been the subject of controlled study. Further experience has been gained in the use of anti-malarials such as the various salts of chloroquine. There has also been some revival and reassessment of older therapeutic agents, particularly gold. Long-accepted methods in physiotherapy and physical measures employed for palliative treatment in the rheumatic diseases have received some hostile criticism. The value of

hospitalization has been assessed, together with social and psychological factors which influence the long-term prognosis in chronic arthritis (Duthie *et al.*, 1955).

PHYSIOTHERAPY

The employment of various forms of physiotherapy, long used in the symptomatic treatment of arthritic patients, has received some criticism (Hamilton *et al.*, 1959). The frequent uncritical employment of such methods has perhaps made them suspect for some time. There can, however, be little doubt about the value of active muscle re-education and re-training, of graduated postural limb movements, together with appropriate splinting in the general programme of physical rehabilitation. It has been suggested, however, that the various forms of electrical treatment contribute little, if anything, and that the application of heat such as infra-red, short-wave diathermy, wax baths, and the like, has little more value than as a pleasant soothing prelude to the more exacting efforts which the patient must be called upon to make and which are necessarily involved in the exercises for stiff and painful joints. It must be agreed that the claims for so-called cure by means of the various applications of heat and of ionization are unwarranted in arthritic diseases, which are so liable to undergo partial or complete spontaneous remission. Nevertheless, it seems likely that the application of heat will continue to be employed for symptomatic relief in certain stages of joint disability. In this limited sense such procedures can be justified and seem likely to continue.

In the physiotherapeutic field some enthusiasm has developed for what has been designated *connective tissue massage* (Dicke, 1953; Ebner, 1956). This is a form of massage with as yet unproven anatomical and physiological implications. It is applied for its circulatory effects, and where circulatory deficiencies exist in the rheumatic and pararheumatic diseases it has a potential field of application.

It is claimed that the method influences the components of the connective tissue system, together with its fluid and other constituents in muscle and subcutaneous tissue, thereby influencing the capillary circulation, which is itself under chemical and nervous influences. This specialized massage, when directed to particular sites, it is believed, increases the peripheral circulation by its stimulating action on the capillaries mediated through a nervous reflex mechanism involving afferent and efferent autonomic pathways through the posterior root ganglion, cord, sympathetic ganglion, anterior roots, to the peripheral cutaneous and subcutaneous areas. A more simple axon reflex mechanism may also play a part in the vascular response of this form of massage, whilst antidromic impulses may represent yet another pathway inducing peripheral vasodilatation effects within corresponding dermatome.

The method of stroking massage is applied to various regions of the back as well as peripherally by a physiotherapist trained in the method. Certainly the circulation in the cold peripheral limbs in rheumatoid arthritis and certain of the pararheumatic diseases can be improved and pain relieved. The objective changes in skin temperature, which may be recorded before and after treatment, can be demonstrated.

GENERAL MEASURES

The value of supportive measures of rest and exercises at appropriate stages, of environmental optimism, and of attention to the general health of the arthritic patient, has always been recognized as a valuable and worthwhile part of the general programme of treatment. It is equally agreed that these measures have only a palliative or symptomatic value. Of similar importance is the need for a dietary survey of adequate protein and vitamin intake for the undernourished and asthenic types, and the treatment of obesity, especially in the chronic osteoarthritic types. Patients commonly believe that diet has something to do specifically with arthritis, but there is no rational foundation for this belief.

A survey of the general health of the patient often draws attention to the existence of a mild to moderately severe hypochromic anæmia which is classically associated with many cases of rheumatoid arthritis. The problem of anæmia in rheumatoid arthritis has been systematically and painstakingly investigated by workers in this country (Duthie *et al.*, 1958; McCrea, 1958), but the cause remains obscure. One factor which should not be overlooked and which has come to the forefront recently is that of unsuspected chronic gastro-intestinal blood loss associated with the consumption of aspirin drugs. Large numbers of patients complain of dyspepsia when taking aspirin and the occurrence of an erosive gastritis as a basis for this was demonstrated many years ago (Douthwaite and Lintott, 1938). Recently, controlled studies concerned with the presence of occult blood in the stools of patients taking aspirin for a variety of reasons, have thrown further light on this subject.

Avery Jones and his colleagues (1959), in a recent follow-up of over 2,500 cases of gastro-intestinal bleeding, found that 20 per cent. of them had no x-ray or other evidence of the cause of the bleeding. From the same department Alvarez and Summerskill (1958) found that 49 out of 103 admissions for hæmatemesis had been taking a salicylate preparation and these cases had a higher proportion of positive occult blood tests in the stools compared with other patients who were taking non-salicylate analgesics.

They thus confirmed an earlier observation of Muir and Cossar, in 1955, that this mechanism of gastro-intestinal blood loss makes a significant contribution to those cases of x-ray negative hæmatemesis and melæna, and may constitute up to 40 per cent. of them. Avery Jones and his colleagues concluded that, among these cases, 'aspirin plays a very significant etiological role' in the cause of alimentary blood loss. The importance of this observation for rheumatologists in relation to their almost universal aspirin-taking patients who have a chronic hypochromic anæmia scarcely needs further comment. It would seem, however, that all investigations into the anæmia of rheumatoid arthritis must exclude this now obvious possibility.

Meanwhile the pharmaceutical drug houses have been active in producing analgesic substitutes for aspirin, some of them simple modifications of aspirin itself or of phenacetin and others having no structural relationship to either. They all claim to cause no gastric upset in patients who have this

disturbance when taking ordinary aspirin. The simple solution of using soluble aspirin, or aspirin taken together with an antacid, does not seem to be the practical answer to this problem. Aspirin combined with an antacid, the so-called 'buffered' aspirin, has been criticized adversely in this connexion, by Batterman (1958) and Cronk (1958), who conclude that it is doubtful if the claim that such a preparation causes less gastric disturbance than aspirin itself can be substantiated. Enteric-coated tablets containing aspirin and its near relatives have been tried, but there is the difficulty of non-disintegration. Glycine mixed with aspirin which aids in its rapid disintegration was introduced, but Lange (1957) showed this compound tablet to have no difference in its liability to cause positive occult blood tests in the stools. Some of the more recently introduced non-salicylate-containing analgesics have yet to prove themselves as effective substitutes. Trials with these drugs are proceeding and the matter is still *sub judice*.

PHENYLBUTAZONE

Phenylbutazone has now an established place as an analgesic in the symptomatic treatment of rheumatoid arthritis, spondylitis, osteoarthritis, and gout. Bauer has emphasized its value in spondylitis. Its toxic effects in larger doses may be considerable, and even smaller doses are sometimes not well tolerated. Thus, it occasionally causes fluid retention with œdema, seen most prominently in the lower limbs, occasionally sore mouth, nausea, vomiting, dyspepsia, reactivation of peptic ulcer with hæmorrhage or perforation, diarrhœa, vertigo, insomnia and, rarely, serious blood dyscrasias. There has followed a tendency to use a slightly lower dose than that originally recommended. In many cases a dose of 100 mg. three times a day will suffice; a dose of 400 mg. in divided doses is rarely exceeded, but it may be doubled for one day to get a rapid analgesic effect in acute gout and, having obtained relief of pain in this disorder, the dose is quickly reduced. In the treatment of rheumatoid arthritis it has been combined with salicylates: in a well-controlled trial (Kern *et al.*, 1957) it appeared to be a worth-while addition to the good general régime which included salicylates, and to shorten the period of disability. Several analogues or metabolites of phenylbutazone are under trial, and at least one of them, G.28.315 ('anturan'), appears to be a valuable addition as a uricosuric agent, which is also mildly analgesic for the prolonged treatment of chronic tophaceous gout (Kersley *et al.*, 1958); in my experience it is superior to probenecid for this purpose. Phenylbutazone, in a dose of 50 mg., has recently been combined with 1.25 mg. of prednisone in a single tablet. Whether this combination is safe and satisfactory is at present under trial.

CHLOROQUINE IN RHEUMATOID ARTHRITIS

It is an unfortunate testimony to the still unsatisfactory state of therapy in rheumatoid arthritis that on such slender and uncontrolled evidence as is available, anti-malarial drugs could gain a place in the treatment of rheumatoid arthritis. The fact that they have done so calls for brief consideration.

The original observation that mepacrine, used in a case of chronic lupus erythematosus, was associated with some improvement in an accompanying joint disturbance was the starting point. This drug, because of its yellow staining of the skin and tendency to cause occasional agranulocytosis, was abandoned in favour of chloroquine. Various salts of this preparation are in current use. In rheumatoid arthritis the dosage is usually 250 mg. twice a day. Perusal of Bagnall's article, published in 1957, does not carry much conviction.

> He treated a variety of arthritic patients suffering from 'rheumatoid disease'. The majority had had continuous treatment for more than a year, a minority for more than two years, and during this time all were receiving physiotherapy, rest, sedation, and salicylates, whilst more than a third were given steroids in unstated doses and for unstated periods. Remission or improvement in the arthritis was claimed to have occurred in the inevitable 70 per cent. The author considered that at least six to twelve months' treatment was required in order to obtain the maximum degree of improvement. Toxic reactions attributed to chloroquine therapy include dermatitis, nausea, vomiting, vertigo, at some stage in as many as one-third of the patients, less frequently leucopenia and lymphœdema. The dosage of chloroquine had to be reduced in one-third of the patients and in 10 per cent. stopped altogether.

The list of toxic disturbances has had further additions. Thus, disturbances of vision, coloured lights, blurring with deposits in the corneal epithelium have been noted, and actinic erythema, bleaching of the eyebrows and hair, suggest that chloroquine may interfere with normal skin pigmentation. These toxic disturbances have been seen at dosage levels usually recommended for chloroquine therapy in arthritis, which is from about 400 to 600 mg. a day (Rinehart *et al.*, 1957). Bagnall's provisional view that chloroquine is one of the safest agents for long-term control of rheumatoid arthritis and for the prevention of relapses must be viewed with considerable scepticism (Erlendsson, 1958). As an occasional alternative choice for long-term therapy in certain cases of rheumatoid arthritis chloroquine is still under trial in our unit, but from observations over a two-year period it has hardly justified continued use.

THE PRESENT POSITION OF GOLD THERAPY

Many rheumatologists, both in this country, the Continent and the Americas, continue to use and report favourably upon gold for the long-term treatment of rheumatoid arthritis (Freyberg, 1957; Lockie *et al.*, 1958; Smith *et al.*, 1958). In many cases, but not all, gold helps to reduce activity, and a large number of critical clinicians believe that it has sufficient value to merit continued use. It had been used for about twenty years before cortisone appeared, and the hope that steroid therapy would eventually be so superior that gold would cease to be used has not in fact been realized. For the doctor who proposes to use the modified gold treatment as commonly employed today, the following facts should be borne in mind. There must be a familiarity with what gold will and will not do; familiarity with the toxic disturbances, less frequent and less severe on the modern smaller dosage; the warning of the development of toxic upset; the knowledge that improve-

ment in arthritis can only come about slowly; the right type of case must be selected, that is one showing some activity of the disease but before advanced erosive and crippling changes have occurred, for gold will not influence burnt-out rheumatoid arthritis; it must be appreciated that a smaller dosage schedule and a more prolonged course with later spaced maintenance treatment is an important modification; and finally that good to excellent results may be achieved in many, but not all, cases of rheumatoid arthritis.

The only agents having the capacity to suppress rheumatoid activity are gold and the steroids, and to choose between them is not always easy, for, whereas gold achieves its effects more slowly and with less certainty, there will usually be longer sustained benefit and less disturbing and fairly well-controlled adverse side-effects. On the other hand, it must be recognized that, whilst corticosteroids are more powerful and rapid in their initial suppression, they possess potentially more serious side-effects. Thus, today the prospective candidate for gold treatment is one whose disease is not fulminating, but remains active and slowly progressive after, say, three to six months of conservative treatment, is young and otherwise healthy, and without a history of allergy or drug sensitivity. Others for whom gold therapy may be considered are patients who have progressive rheumatoid disease associated with peptic ulcer, severe hypertension, diabetes mellitus or recent psychoses, for whom the corticosteroids would be contraindicated.

The choice of the gold preparation, given by weekly intramuscular injection, is of a soluble gold salt, such as sodium aurothiomalate or gold sodium thioglucose, both of which contain approximately 50 per cent. of gold. The first two injections are of 10 and 25 mg. respectively at weekly intervals, and thereafter 50 mg. weekly until about twenty injections have been given. After this, maintenance treatment is instituted, which means four to six injections at two-weekly intervals and a further four to six at three-weekly intervals, and thereafter a monthly injection for a year or more. The injections are stopped only when it is clear that activity is completely suppressed and nothing further is to be gained by continuing them. This modified plan of dosage, including prolonged maintenance treatment, was developed in the United States and has been shown to reduce the relapse rate when comparison is made with the older method of giving a course of twelve weekly injections (of larger dosage) and then stopping for three months, resuming a second course of twelve injections and again a three months' interval and possibly a third course if necessary. On the now accepted plan of smaller dosage toxicity is much less severe and less often seen but, should it occur, the gold must, of course, be promptly discontinued. If the toxic reaction is mild little else is required, but if serious the antidote is dimercaprol: four to six injections on the first day, and then two or three injections for a further two or three days. The availability of steroids and of corticotrophin is also to be noted, for they are dependable agents for the treatment of gold toxicity and avoid the undesirable features which sometimes accompany the use of BAL.

ANTI-INFLAMMATORY STEROIDS

The search for the ideal anti-inflammatory steroid continues. The advantages of such a preparation, devoid of all unwanted side-effects, maintaining the rheumatoid patient in safety without losing its effect, is the goal which urges on many teams of pharmacologists and structural chemists. By rearranging and modifying the various side-groups around the original hydrocortisone

Side effects	Steroid				
	Cortisone and hydrocortisone	Prednisone and prednisolone	Methyl-prednisolone on full dose	Triamcinolone on full dose	Dexamethasone and Hexamethasone on full dose
Sodium retention; œdema; gain in weight	+ + +	+ +	+	+ +	+
Potassium loss	+ + +	+ +	+	+	+
Mooning of face	+ +	+ +	+ +	+ +	+ +
Hypertension	+ +	+	—	±	±
Nitrogen balance	—	—	—	—	—
Gastro-intestinal ulceration	+	+ + +	+	+ +	+
Bleeding tendencies	+	+	—	?	+
Insomnia; psychotic episodes	+	+	+	?	?
Super-infection (rare)	+	+	+	+	+
Special features				Muscle-wasting Flushing Headaches Dizziness Nausea Loss of weight	? depression of thyroid function
Relative dose	Cortisone 125 Hydrocortisone 100	Prednisone 30 Prednisolone 25	20	25	4

TABLE I.—Table showing the relative potency of the anti-inflammatory steroids used in the rheumatic diseases together with a comparison of the common side-effects as judged from the author's experience and a survey of the literature.

structure, a number of new substances have been developed and have undergone clinical trial. The removal of the double bond between 1 and 2 position in both cortisone and hydrocortisone produced the 1-dehydro or 'predni' preparations, prednisone and prednisolone. It was perhaps a little surprising that the introduction of the atom fluorine into the 9 position enormously enhanced the anti-inflammatory effect. In their review of 'Advances in Endocrinology' in this issue (p. 425) Cope and Harrison discuss the subject with great clarity. Clearly a most fruitful line of research has been developed on the relationship between structure and function, and we are by no means at the end of all possibilities.

In recent months clinical trials among rheumatic patients have been completed with these newer derivatives, including triamcinolone (Hart *et al.*, 1958; Hartung, 1958; Thompson, 1959), dexamethasone (Bunim *et al.*, 1958) and methylprednisolone (Boland and Liddle, 1957). A comparison of the strength and physiological function of these newer synthetic steroids

cannot be reviewed in detail here, but table I shows in summarized form the main physiological properties and the relative strengths, together with some new and old side-reactions which have been encountered. Increasing strength in an anti-inflammatory sense is not enough if the unwanted side-effects still persist. The initial claims for each new product have not always been substantiated, but it seems clear that the more gross salt-retaining and potassium-losing features, characteristic of cortisone and hydrocortisone, may have been partly modified. It is still possible, however, when larger doses of these newer products are used, for these unwanted features to make their appearance. Thus mooning, sometimes gross, and more generalized œdema are seen with prednisone and prednisolone when full doses are used (Cohen *et al.*, 1957; Stolzer *et al.*, 1957; Ward *et al.*, 1958), and, in spite of what has been claimed for them, methylprednisolone (Boland and Liddle, 1957; McMahon and Gordon, 1958), triamcinolone (Zuckner *et al.*, 1958), and dexamethasone (Boland, 1958), have all caused similar phenomena. There is some evidence that dexamethasone has anti-thyroid effects and that capillary damage may be a factor in œdema, as well as the purpura which has been observed. On more restricted and usual doses, however, the development of hypertension and œdema, for practical purposes, does not occur, and the last three preparations seem to be a small advance to counter such features if they represent a potential hazard in a given patient. As to the advantages in practice of these newer anti-inflammatory steroids, one over the other, it is difficult to be more explicit than to quote the view expressed by the panel of distinguished medical advisers to Drug and Therapeutics Information, Inc., that 'there is nothing to choose between them'.

When it seems essential that the dose of a given steroid should be maintained, a minor degree of modification of unwanted side-reactions may be obtained by some of the following methods (Slocumb *et al.*, 1957). Œdema and gain in weight may be countered by a low-sodium diet permitting less than 500 mg. daily, together with the administration of potassium as potassium chloride 1 g. three times a day. Chlorothiazide, 0.5 g. three times a day, with the supplementary potassium, both given one day each week, will be helpful. This procedure, however, although helping the general œdema and body weight, does not appear to alter the degree of facial mooning due to redistribution of facial fat. The rare severe hypokalæmic effects with weakness, ascending paralysis, poor heart sounds and electrocardiographic changes can be completely prevented by the administration of potassium. The negative nitrogen balance due to the catabolic effect of the anti-inflammatory steroids is an indication of loss of body protein and an important factor in the production of the long-term osteoporosis seen more particularly in post-menopausal women, but also amongst other patients. To counter this, combinations of œstrogens and androgens have been used, but the more recently developed anabolic steroid, norethandrolone, is under trial and would appear to be preferable for restoring this defect in the bony matrix. This preparation, however, in spite of what is claimed, does not

avoid the masculinizing effects which it was claimed to do. Combined with oral calcium and vitamin D, long-term steroid osteoporosis should theoretically be favourably influenced. Striæ which are seen in long-term high-dosage steroid therapy, especially in children, represent the effect on connective tissue metabolism, and respond only to diminution of the dose together with the administration of anabolic agents. No undue alarm need be felt at the appearance of transient glycosuria, and in many cases there is no significant elevation of fasting blood sugar (Zuckner *et al.*, 1958). If the patient is an unsuspected but potential diabetic and the fasting blood sugar rises above 130 mg. per cent., insulin should be employed if steroid therapy is to be continued. Cutaneous bruising and slight bleeding tendencies, noted particularly with prednisone and prednisolone, are thought to be due to leakage from smaller vessels produced by partial destruction of the muscular and elastic tissues (Nashelsky and Smyth, 1958). There is no change in platelets and there is no effective counter measure. Fortunately, it is not usually of much significance, other than its unsightliness. Gastro-duodenal ulceration (Kern *et al.*, 1957) with increased gastric acidity, more obvious with the introduction of the 'predni' steroids, can sometimes be minimized or modified by the judicious use of antacids and anticholinergic drugs and keeping the dose of steroid as low as possible (West, 1958). Acne, hirsuties and amenorrhœa usually respond to symptomatic treatment together with the gradual reduction of the steroid.

The troublesome withdrawal symptoms may be minimized by the gradual reduction of the dosage of the steroid. In the early period of reduction there will usually be a return of pain and stiffness for a variable period of from one to three weeks. During steppage reduction it is useful to remember that the optimum time for administration of a single daily dose is between 08.00 and 09.00 hours, which covers the relatively deficient autogenous adrenal secretion at its lowest ebb during the morning hours. The use of slow intravenous corticotrophin drips or gel may help to minimize the duration of early severe withdrawal symptoms, but the whole pituitary-adrenal secretory mechanism may take as long as six months to get back to normal from the time when the supply of exogenous steroid was stopped. Because of the special hazard, most patients on long-term steroid therapy in rheumatism clinics are supplied with a special card which they carry with them, indicating the fact that they are steroid-treated patients, giving personal and hospital particulars, the date and dosage of the preparation, and a warning what to do in an emergency, in intercurrent medical illness, always to seek medical advice before changing the dose, and to keep a reserve supply of steroid tablets constantly available.

INTRA-ARTICULAR THERAPY

The use of the natural and synthetic steroids locally for anti-inflammatory purposes has a wide application in medicine. In the chronic rheumatic diseases it has found a permanent place in the treatment of joints by intra-

articular injections. It is also symptomatically helpful in some soft-tissue lesions such as tennis elbow, flexor tendonitis, and the like. The method was first applied to the larger joints (Hollander *et al.*, 1951, 1955). Smaller joints also, such as those of the fingers, have been injected with benefit (Wright, 1958). Recent clinical trials have attempted to assess the value of the method, the existence of possible hazards, the specific indications and the most effective preparations.

Hydrocortisone acetate was used originally for intra-articular injections and the consensus of opinion was that considerable symptomatic benefit, with partial or complete relief of pain and stiffness, was usually achieved. Further experience of the method has tended to show that the duration of relief was often all too brief. Thus, Duff (1956) reported benefit for only seven to ten days in 50 per cent. of his cases. On the basis of a purely local anti-inflammatory effect, the theoretical view has been developed that the most useful preparation would be non-irritating and of low solubility, so that it would act *in situ* for a long period without systemic absorption. The more powerful the anti-inflammatory preparation per unit dose, the more effective is it likely to be. These views have led to the trial of other preparations, such as, for example, a micro-crystalline suspension of prednisolone and trimethylacetate, which Murdoch and Will have recently claimed (1959), on the basis of a double-blind trial, to compare favourably with the original hydrocortisone. They also claim that, compared with hydrocortisone, it is more effective in terms of reversal of synovial-fluid abnormality and that it is superior to other steroids for intra-articular injection. In periarthritis of the shoulder, Lloyd-Roberts and French (1959) considered that in early cases an injection of hydrocortisone after manipulation under anæsthesia, together with standard routine physical methods, reduced the total period of disability to a greater extent, compared with a similar series of cases identically treated except that oral cortisone was given instead of the intra-articular hydrocortisone injection into the shoulder joint.

In our own clinic, we (Chandler *et al.*, 1958; Chandler and Wright, 1958) have carried out a strictly controlled double-blind trial using 24 patients with comparable arthritis of the knees, carefully comparing hydrocortisone acetate with hydrocortisone tertiary-butylacetate, which was reputed to be longer acting than hydrocortisone acetate.

The effective difference between the two preparations was hardly statistically significant. Moreover, we observed a tendency to disquieting radiological deterioration in the injected joints, some of which (13 out of 25), after repeated injections with the active steroid, showed the apparent paradox of worsening of the disease in weight-bearing joints, in the face of temporary clinical improvement. Another case, not in the series, has been reported (Chandler *et al.*, 1959) in which repeated intra-articular injections into an osteoarthritic hip-joint had been almost too successful in suppressing pain. The patient remained actively ambulant, but in the course of one-and-a-half years progressive, rapid and painless deterioration of the joint was seen on repeated x-ray examination, the appearance and clinical behaviour resembling a Charcot arthropathy.

It would seem a wise precaution therefore that in weight-bearing joints

intra-articular injection should not be carried out too often, and when joints are injected more than three times successively, radiological control is desirable.

THE PARARHEUMATIC DISEASES

In this group of serious and often fatal diseases, which form a spectrum of varying and intermixed symptomatology according to the anatomical location of the connective tissue lesion, there has been no significant therapeutic advance. The general measures are as for those of rheumatoid arthritis. Hormone treatment is of limited value, but some authorities have thought that triamcinolone has become the slightly preferable steroid in the treatment of disseminated lupus erythematosus. Usually high doses and the accompanying side-reactions have to be tolerated, and they seem to affect females rather more than males (Dubois, 1958), with progressive loss of weight, some of which doubtless was fluid, and of muscle weakness, especially of the quadriceps. In the absence of any specific alternative, the treatment of *lupus erythematosus* is extremely unsatisfactory. The possibility of a remission can always be hoped for, but it is not common, and if steroid therapy is used it seems probable at the present time that triamcinolone should be selected.

The incidence of *polyarteritis nodosa* seems to be slightly increasing among patients suffering from rheumatoid arthritis and there is a suggestion that this may be associated with, or in fact due to, steroid therapy. Kemper and his colleagues (1957) have produced post-mortem evidence suggesting that in certain susceptible patients with rheumatoid arthritis diffuse arteritis may follow the administration of cortisone. A similar view has been expressed in regard to the appearance of L.E. cells in arthritic patients, and both are regarded as an abnormal mesenchymal response to steroid therapy.

On the whole, in *polyarteritis nodosa*, *disseminated lupus erythematosus*, *dermatomyositis* and *scleroderma*, hormones seem to be of little value, and the justification for their employment is usually that no other alternative treatment for these members of the collagen group or pararheumatic diseases is available. Occasionally therefore steroids and corticotrophin are used, perhaps particularly for advanced and fulminating types, and from time to time transient temporary remissions in the clinical picture have been recorded.

References

Alvarez, A. S., and Summerskill, W. H. J. (1958): *Lancet*, **ii**, 920.
Bagnall, A. W. (1957): *Canad. med. Ass. J.*, **77**, 182.
Batterman, R. C. (1958): *New Engl. J. Med.*, **258**, 213.
Bauer, W., and Ropes, M. W. (1956): *The Practitioner*, **177**, 431.
Black, R. L., Yielding, K. L., and Bunim, J. J. (1957): *J. chron. Dis.*, **5**, 751.
Boland, E. (1958): *Ann. rheum. Dis.*, **17**, 378.
——, and Liddle, G. W. (1957): *Ibid.*, **16**, 297.
Bunim, J. J., Black, R. L., Lutwak, L., Peterson, R. E., and Whedon, G. D. (1958): *Arthritis and Rheumatism*, **1**, 313.

Chandler, G. N., Hartfall, S. J., and Wright, V. (1958): *Lancet*, **ii,** 659.
——, ——, Jones, D. T., and Wright, V. (1959): *Brit. med. J.*, **i,** 952.
——, and Wright, V. (1958): *Lancet*, **ii,** 661.
Cohen, A., Turner, R. F., Kanenson, W. L., and Goldman, J. (1957): *J. Amer. med. Ass.*, **165,** 225.
Cronk, G. A. (1958): *New Engl. J. Med.*, **258,** 219.
Dicke, E. (1953): 'Meine Bindegewebsmassage', Stuttgart.
Douthwaite, A. H., and Lintott, G. A. M. (1938): *Lancet*, **ii,** 1222.
Dubois, E. L. (1958): *J. Amer. med. Ass.*, **167,** 1590.
Duff, I. F. (1956): *Postgrad. Med.*, **19,** 577.
Duthie, J. J. R., Richmond, J., Roy, L. M. H., Gardner, D. L., and Alexander, W. R. M. (1958): *Ann. rheum. Dis.*, **17,** 406.
——, Thompson, M., Weir, M. M., and Fletcher, W. B. (1955): *Ibid.*, **14,** 133.
Ebner, M. (1956): *Brit. J. phys. Med.*, **19,** 176.
Erlendsson, F. (1958): *Ugeskr. Læg.*, **120,** 793, 800, 804.
Freyberg, R. H. (1957): *J. chron. Dis.*, **5,** 723.
Hamilton, D. E., Bywaters, E. G. L., and Please, N. W. (1959): *Brit. med. J.*, **i,** 542.
Hart, F. D., Golding, J. R., and Burley, D. (1958): *Lancet*, **ii,** 495.
Hartung, E. F. (1958): *J. Amer. med. Ass.*, **167,** 973.
Hollander, J. L., Brown, E. M., Jessar, R. A., and Brown, C. Y. (1951): *Ibid.*, **147,** 1629.
——, Udell, L., Smuckler, N. M., and Bowie, M. A. (1955): *Ibid.*, **158,** 476.
Jones, F. Avery, Read, A. E., and Stubbe, J. L. (1959): *Brit. med. J.*, **i,** 1138.
Kemper, J. W., Baggenstoss, A. M., and Slocumb, C. H. (1957): *Ann. intern. Med.*, **46,** 831.
Kern, F., Clark, G. M., and Lukens, J. G. (1957): *Gastroenterology*, **33,** 25.
Kersley, G. D., Cook, E. R., and Tovey, D. C. J. (1958): *Ann. rheum. Dis.*, **17,** 326.
Lange, H. F. (1957): *Gastroenterology*, **33,** 770.
Lloyd-Roberts, G. C., and French, P. R. (1959): *Brit. med. J.*, **i,** 1569.
Lockie, L. M., Norcross, B. M., and Riordan, D. J. (1958): *J. Amer. med. Ass.*, **167,** 1204.
McCrea, P. C. (1958): *Ann. rheum. Dis.*, **17,** 89.
McMahon, F. G., and Gordon, E. S. (1958): *J. Amer. med. Ass.*, **168,** 1208.
M.R.C. and Nuffield Foundation Joint Committee (1957a): *Brit. med. J.*, **i,** 847.
—— (1957b): *Ibid.*, **ii,** 199.
Muir, A., and Cossar, I. A. (1955): *Ibid.*, **ii,** 7.
Murdoch, W. R., and Will, G. (1959): *Ibid.*, **i,** 1267.
Nashelsky, G. M., and Smyth, C. J. (1958): *Ann. rheum. Dis.*, **17,** 76.
Rinehart, R. E. (1957): 'Eleventh International Congress on Rheumatoid Diseases', Toronto.
——, Rosenbaum, E. E., and Hopkins, C. E. (1957): *Ibid.*
Slocumb, C. H., Polley, H. F., Ward, L. E., and Hench, P. S. (1957): *Ann. intern. Med.*, **46,** 86.
Smith, R. T., Peak, W. P., Kron, K. M., Hermann, I. F., DelToro, R. A., and Goldman, M. (1958): *J. Amer. med. Ass.*, **167,** 1197.
Stolzer, B. L., Barr, J. H., Eisenbeis, C. H., Wechsler, R. L., and Margolis, H. M. (1957): *Ibid.*, **165,** 13.
Thompson, M. (1959): *Brit. med. J.*, **i,** 1259.
Ward, L. E., Polley, H. F., Power, M. H., Mason, H. L., Slocumb, C. H., and Hench, P. S. (1958): *Ann. rheum. Dis.*, **17,** 145.
West, F. H. (1958): *Ibid.*, **17,** 273.
Wright, V. (1958): *Acta rheum. scand.*, **4,** 40.
Zuckner, J., Ramsey, R. H., Caciolo, C., and Gantner, G. E., Jr. (1958): *Ann. rheum. Dis.*, **17,** 398.

ADVANCES IN THE TREATMENT OF VENEREAL DISEASE

By AMBROSE J. KING, M.B., F.R.C.S.

Senior Physician, The London Hospital Clinic for Venereal Diseases

THE efficacy of methods of treatment of the venereal diseases is apt to be judged not only by the results obtained in the treatment of individual patients, but also by the rise or fall in incidence of the diseases in relation to the employment of new remedies.

INCIDENCE

In England and Wales (Ministry of Health, 1958) the number of new cases of syphilis in all stages attending the public clinics fell from 23,878 in 1946 to 4,977 in 1957. During the same period the number of cases of early, and presumably infectious, syphilis fell from 17,675 to 747. A similar spectacular decline in incidence has occurred in many western countries and has been thought to be the direct result of modern treatment with penicillin. No doubt, improvements in treatment have contributed to these satisfactory circumstances, but many complex factors determine changes in the prevalence of venereal infections and some of them are at least equal in importance to the effects of treatment. Moore, in 1951, produced evidence that the prevalence of syphilitic infection had steadily declined in western countries since at least 1860, although there had been transitory increases of almost epidemic character associated with wars, political unrest and movements of populations. Allowing for these peaks the decline had been progressive for ninety years, apparently uninfluenced by public health measures directed to the 'control' of syphilis, including treatment in the form of metal chemotherapy, and also—up to 1949 at any rate—penicillin. He reached the conclusion that the decline depended upon the general improvement in socio-economic conditions accompanying the industrial revolution. Continuing this discussion in 1956, he noted that this decline had continued, to reach an unprecedented and still declining low level in 1952 to 1955. No-one could say whether this was due to the widespread use of penicillin in the treatment of syphilis. He and others were inclined to think that the treatment of syphilis with penicillin was less important in this respect than the widespread use of penicillin and other treponemicidal antibiotics for almost every human ailment.

If there were grounds for supposing that new remedies had solved the problem of syphilis, it seemed that the prospects of eliminating gonorrhœa were still more hopeful. The organism was extremely susceptible to penicillin and other antibiotics, in comparatively small doses, and the response to treatment was prompt and most satisfactory. The number of cases

attending the public clinics fell from 47,343 in 1946 to 17,536 in 1954, but since then there has been an increase year by year and in 1957 the number reached 24,381.

DIAGNOSIS OF SYPHILIS

When this subject was last reviewed three years ago (King, 1956) reference was made to the clinical application of the treponemal immobilization test (T.P.I.) for syphilis, and to the search for other tests, depending upon the same specific antibody, which might be less complicated and less expensive. In the intervening period several tests have been devised, none of which seems likely to replace the T.P.I. test. There are, however, considerable hopes that the so-called Reiter protein complement fixation test (R.P.C.F.T.) may prove a reliable and economical procedure, more specific than the standard serological tests and approaching the accuracy of the T.P.I. test in distinguishing between positive standard serological reactions due to syphilis and those due to other causes. The antigen employed is a protein fraction derived from the non-specific Reiter's strain of *Treponema pallidum*. This strain can be grown inexpensively in simple culture media.

PREVENTIVE TREATMENT OF SYPHILIS

The case for and against the abortive treatment of syphilis was considered in 1956, and need not be reviewed in detail. It cannot be said too often that 'diagnosis before treatment' is a fundamental rule and departures from it must be carefully considered, and undertaken reluctantly. To give abortive treatment is tantamount to accepting the diagnosis of syphilis, yet leaving the patient in a position of damaging uncertainty. Observation and testing must be as prolonged and complete as if the disease had certainly been present, and these procedures may prolong for years anxiety which could be limited to three months. It brings into family life prohibitions and stresses which may well destroy marriage.

CURATIVE TREATMENT OF SYPHILIS

Penicillin remains the drug of choice for the treatment of syphilis. Increasing experience serves only to confirm that it is by itself highly effective and that the addition of other drugs adds nothing to the excellence of results of treatment. It seems true to say that the use of the organic arsenicals is no longer justifiable and that injections of bismuth have only limited value as preliminary treatment in some cases of late syphilis.

The best results are obtained with continuous prolonged concentrations of penicillin in the circulating blood, but high concentrations appear to be unnecessary. The repository preparations are ideal for the purpose, and procaine penicillin, in oily or watery suspension, may be given daily in doses of 600,000 units; but the standard remedy is still procaine penicillin in oily suspension to which has been added 2 per cent. of aluminium mono-

stearate (PAM). This may be given daily in doses of 600,000 units, but such a dose will usually maintain an effective blood level for 72 hours, making it feasible to give an injection every two or three days, if necessary. Daily administration, on the other hand, has the advantage that it produces numerous slowly absorbed deposits which prolong treatment for an appreciable period after injections have been discontinued.

In the treatment of *early syphilis* 10 daily injections, each of 600,000 units, of PAM or of procaine penicillin in watery suspension, suffice to cure more than 95 per cent. of cases. Some prefer to begin with a single large dose of PAM, such as 2.4 mega units, in case the patient fails to return for further treatment. With such a dose infectiousness can be controlled and there is a chance of cure. Patients who cannot attend or who are unlikely to cooperate may be given a single intramuscular injection of 2.5 mega units of benzathine penicillin, which provides an effective level of penicillin in the blood for two weeks or more and has been shown to be as effective as a single course of injections of procaine penicillin G in oil totalling 4.8 mega units. It has the disadvantage that the injections are apt to be painful, which still further discourages the uncooperative patient.

In the treatment of *late syphilis* of the *benign gummatous type*, and of *late latent syphilis* in which there is no other evidence than the positive serological tests, the same treatment is effective and there seems no need to prolong it. Whether it is a useful precaution to start with intramuscular injections of bismuth seems to be a matter of some controversy. If penicillin is given at once there is probably a slight danger from the Jarisch-Herxheimer reaction if there are undiscovered foci of active syphilitic infection in certain areas, such as the aortic wall, the openings of coronary arteries, in large cerebral vessels or round the larynx. The reaction cannot be prevented by starting with small doses of penicillin but seldom occurs if intramuscular injections of insoluble bismuth are given in doses of 0.2 to 0.3 g. weekly for three to four weeks. It should be said that these reactions are rare in cases of late syphilis and many physicians have started treatment with penicillin and seen no ill-effects. Nevertheless, there is no indication for speed and a potentially serious reaction, however uncommon, which is preventable, should be prevented. If bismuth is contraindicated by kidney disease or oral sepsis, the slight risk of using penicillin at once should be taken.

In the treatment of *cardiovascular syphilis* assessment of the value of antisyphilitic treatment is difficult because of the varied character of the lesions and the uncertainty of the prognosis in individual cases. General measures are of great importance and if the patient's occupation is physically strenuous he should be advised to change it. Antisyphilitic treatment may be expected to bring about healing of active lesions and to prevent progression, but damage to the aortic wall is permanent and complications may result from the scarring which follows healing. It is advisable to

begin treatment with injections of insoluble bismuth, although evidence from the United States has suggested that the value of this precaution has been exaggerated. Daily injections of a preparation of procaine penicillin may be given for ten to fourteen days, with total dosage of 6 to 8.4 mega units, and usually no further antisyphilitic treatment is required.

For *neurosyphilis*, penicillin remains the remedy of choice and fever therapy is seldom required. Daily injections, each of 600,000 units of procaine penicillin, may be given for twenty-one days. In estimating response to treatment, clinical examination is less helpful than tests of the cerebrospinal fluid, which should be done at lengthening intervals over a number of years. Provided that the cell count and the protein content of the fluid become and remain normal, positive Wassermann or equivalent reactions or abnormalities in the Lange test are not indications for further treatment. Additional courses of treatment are seldom required except in some cases of general paralysis. In cases of late syphilis serological tests may well remain positive in spite of all treatment. Such results do not indicate a need for further treatment.

CONGENITAL SYPHILIS

Penicillin, administered to *syphilitic pregnant women*, is most effective in the prevention of congenital syphilis, whether it is given early or late in pregnancy. Ten days of treatment are almost certain to be adequate and, unless the patient is sensitive to the drug, there are no hazards. Thus, congenital syphilis could be almost entirely eliminated if routine serological tests for syphilis were applied as part of antenatal care in all cases. This precaution is observed faithfully at antenatal clinics of hospitals and local authorities, but not always when patients remain under the care of their own doctors. Provided that adequate treatment has been given in the first pregnancy, there is little risk of transmission of infection in subsequent pregnancies. Nevertheless, it is common practice in this country to give an additional course of injections of penicillin in each subsequent pregnancy.

Penicillin is an excellent remedy for *established congenital syphilis* and other remedies are unnecessary. The best results are obtained in the early stages, in the first two years of life. Dosage may be based on body weight. A good working plan is to give 200,000 units of crystalline penicillin per pound of body weight (450,000 units per kg.). Thus, for an infant weighing 7 pounds the total dosage would be 1,400,000 units. If the patient is admitted to hospital injections may be given every three hours, missing one dose at night and spacing the treatment over ten days. The total amount of 1.4 mega units would be given in 70 injections, each of 20,000 units. An alternative method, which saves many injections, is to give procaine penicillin, 150,000 units daily for ten days. In the later stages of the disease the scheme of treatment is similar and dosage is similarly based upon body weight.

In the suppressive treatment of *interstitial keratitis* steroid hormones

have an important place. Ashworth (1958) used cortisone acetate suspension in normal saline (5 mg./ml.), or cortisone ointment (15 mg./g.), or both, by local application to the conjunctival sac. The remedy was applied every two hours until the eye was white and comfortable, which usually took four to five days. Treatment was then given four-hourly. In severe cases with indifferent response, a subconjunctival injection of cortisone (10 mg. in 0.4 ml.) was given in addition. With these methods he was able to establish control in 50 cases in which 84 eyes were affected. The method gave freedom from symptoms, a good expectation of a 6/6 visual acuity, and no corneal scarring, or so little that it did not interfere with visual acuity. The patient was usually retained in hospital for ten to fourteen days and then continued the topical therapy at home. The cortisone was applied four-hourly during the day for four weeks and then gradually reduced to eight-hourly, and then to twice daily. After four more weeks the treatment could be stopped altogether, unless there was some evidence of relapse. Local hydrocortisone (5 mg./ml.), prednisone acetate (0.25 per cent.), and prednisolone free alcohol (0.25 per cent.) have also been used successfully. It is necessary in all these cases to keep the pupil dilated with atropine during the period of treatment. Antisyphilitic treatment is given at the same time but has no effect upon the keratitis.

TOXICITY OF PENICILLIN

Reactions to penicillin are still few but, inevitably, more people are becoming sensitized to a drug which has been used so freely. The first and essential precautionary measure is to ask the patient whether he has had penicillin before and whether it produced some reaction. Such a history can be very helpful although certain patients who are sensitized may well be unaware of the fact. Reactions may be immediate or delayed. Immediate reactions take the form of acute anaphylaxis, which has been fatal in some cases. Delayed reactions may appear from twenty-four hours to several weeks after administration of the drug, and may resemble serum sickness. Common manifestations are pruritus, various rashes, arthralgias, effusions into joints, fever and albuminuria. Exfoliative dermatitis and polyarteritis nodosa have been described.

If there is a history of sensitivity, the drug should not be given. In cases of doubt useful information may be obtained by skin testing, although not all patients who are sensitized give positive tests. Smith (1957) described a single test which he claimed gave an accurate indication of which patients were liable to anaphylactic reactions.

He applied drops of procaine penicillin (300,000 units per ml.) to a skin scratch and to the conjunctival mucous membrane. If there was no reaction to either test within fifteen minutes he gave the injection. Itching, redness, œdema and weal formation of the skin, or itching, watering, redness or œdema of the eye indicated the probability of dangerous sensitization.

For the treatment of acute anaphylaxis, a full dose of adrenaline, 10

minims (0.6 ml.) of a 1: 1000 solution should be given intramuscularly and, if necessary, an intravenous injection of aminophylline, 250 mg. in 10 ml. of sterile water. The patient's airway should be unobstructed and oxygen should be given if there is respiratory distress. Delayed reactions may be treated with antihistamines or, if necessary, with prednisone or prednisolone. Good results have been claimed (Minno and Davis, 1957; Zimmerman, 1957-58) in the treatment of delayed reactions by giving an intramuscular injection of 800,000 to 1,000,000 units of penicillinase, which may be repeated at intervals of three to four days. The place of this remedy in the treatment of immediate reactions has not been assessed and it should not be substituted for accepted remedies.

OTHER ANTIBIOTICS

When a patient has been shown to be sensitized to penicillin, a different antibiotic should be employed, in preference to the use of penicillin in conjunction with the steroid hormones, a procedure which is clearly fraught with dangers. Turner and Schaeffer (1954), investigating the anti-treponemal effect of various antibiotics in rabbits infected with a virulent strain of *Treponema pallidum*, listed the following in the order of their effectiveness:—

(1) Penicillin.
(2) Carbomycin and erythromycin.
(3) Oxytetracycline and chlortetracycline.
(4) Chloramphenicol and streptomycin.

In the human subject streptomycin has been generally recognized as having so little effect on the *Treponema pallidum* that it is regarded as the substitute to be used in a case of gonorrhœa in which treatment with penicillin might mask developing syphilis. Chloramphenicol combines only a moderate anti-treponemal activity with a liability to serious toxic side-effects. Clinical experience in the use of carbomycin and erythromycin is at present insufficient to permit the recommendation of either. Chlortetracycline and oxytetracycline appear still to be the drugs of choice, although neither can be regarded as completely satisfactory substitutes for penicillin.

Rodriquez and his colleagues (1952) treated 101 patients suffering from secondary syphilis with chlortetracycline, and observed them for between twelve and fifteen months. Treatment appeared to have been successful in about 75 per cent. The scheme of dosage employed was 2 g. initially, followed by 2 g. four hours later, then 1 g. every four hours day and night until 70 g. had been given in eleven days. Oxytetracycline has been used on small groups of patients, with results similar to those obtained with chlortetracycline. Irgang and Alexander (1953) gave 2 g. daily for fourteen days. Robinson and Robinson (1951) gave an initial dose of 3 g. followed by 0.5 g. every four hours for fifteen days, a total of 48 g. Baler (1956) avoided the occasional uncertainty of oral medication in syphilitics by using an intramuscular preparation, giving 200 mg. twice daily for ten days.

GONORRHŒA

In 1956 (King, 1956) it was possible to write: 'there is no evidence, *in vitro* or *in vivo*, that strains of gonococci are becoming resistant to penicillin'.

Unfortunately this is no longer true. There is considerable evidence that strains of gonococci which are relatively resistant to penicillin are emerging (King, 1958; Curtis and Wilkinson, 1958; Cradock-Watson *et al.*, 1958). Nevertheless, the majority of patients respond well, although the general tendency is to use higher dosage. Procaine penicillin, 600,000 units in a single injection, is adequate in most cases. If the patient fails to respond or relapses within a few days it is probably better to use another drug, although response to larger doses of penicillin is often satisfactory. Penicillin by mouth is also effective in the treatment of gonorrhœa. Phenoxymethylpenicillin gives higher levels of penicillin in the blood of longer duration than other preparations. Sheil (1956) gave 400,000 units three times daily for three days, with good results. Willcox (1958) gave 2 or 3 mega units by mouth in one or two doses, with good results in the cases of white patients but, oddly, with less satisfactory results when the patients were coloured. The results with benzathine penicillin by mouth are poor and this method should not be used.

Streptomycin gives good results in the treatment of gonorrhœa when given intramuscularly in single doses of one or two grammes. There have been reports of streptomycin-resistant gonococci and there is clinical evidence from Liverpool (Alergant, 1958), where streptomycin has been used as the routine remedy, that they may be becoming more common.

Chloramphenicol, chlortetracycline, oxytetracycline, tetracycline, erythromycin and spiramycin are all known to be effective in the treatment of gonorrhœa. Chloramphenicol has been given by mouth in two doses each of 0.25 g. with an interval of one hour (Brett, 1953); in single doses of 1 g. and of 2 g. (Barrett and Burton, 1953) and in single doses of 3 g. (Butler *et al.*, 1952). Good results were claimed for all these methods but results were better with the larger dosage. In view of the occasional dangerous toxic effects of this drug, its use is not recommended for the treatment of gonorrhœa. There seems little to choose between the tetracyclines given by mouth, but oxytetracycline and tetracycline are probably a little more effective than chlortetracycline. Metzger and his colleagues (1954) gave 1.5 g. of tetracycline in three doses, each of 500 mg., at intervals of six hours, with excellent results. Intramuscular injections of tetracycline were also effective (Perkins *et al.*, 1955), but its use should be confined to those newer preparations which do not cause local pain. Spiramycin has proved effective in multiple doses by mouth (Willcox, 1956): 4 to 12 g. were given in one or two days and, in some cases, single doses of 3 to 4 g.

Gonococcal arthritis of the suppurative variety is now virtually extinct in the British Isles, and it has been realized that the non-suppurative polyarthritis formerly termed gonococcal is, in this country at least, related to a non-specific urogenital infection of unknown cause. This complication, so-called Reiter's disease, is dealt with under 'Non-specific Urethritis'.

Iridocyclitis, in association with gonorrhœa, is well controlled by topical

cortisone which should be used in conjunction with general methods of treatment.

Gonococcal ophthalmia neonatorum responds well to frequent local instillations of crystalline penicillin in water solution in concentration of 1 : 10,000 and also to penicillin administered intramuscularly. The patient should be admitted to hospital with the least possible delay.

CHANCROID

This disease, which is very common in tropical and subtropical countries, is uncommon in this country and is found mainly at seaports where it is probably introduced from abroad. With small early lesions, satisfactory healing may follow local cleansing and the establishment of drainage. Larger and more established lesions require other methods. In general the disease responds well to sulphonamides, streptomycin, chloramphenicol and to the tetracycline group of drugs.

Sulphonamides, such as sulphathiazole and sulphadiazine, may be given by mouth in dosage of 2 to 4 g. at once, followed by 1 g. four times daily until healing is well advanced or complete. This may take ten or fourteen days, or even more. Local sulphonamide applications are effective but should not be used for fear of causing local sensitization with potentially severe effects. Suppurating buboes should not be incised but may be aspirated through healthy skin—on several occasions if necessary. If any treatment is to be successful local drainage must be established and this may necessitate dorsal slitting of the prepuce. Streptomycin intramuscularly gives good results. Injections of 1 g. daily for five days are usually sufficient, but more will be required for a few resistant cases. Oxytetracycline or tetracycline may be given by mouth in dosage of 250 mg. six-hourly until healing is complete. They have the disadvantage that they may mask the early signs of syphilis and, on that account, sulphonamides and streptomycin are preferable. Deacon and his colleagues (1956) claimed good results in the prevention and treatment of chancroids by local application of chloramphenicol cream.

LYMPHOGRANULOMA VENEREUM

Although there is some reason to suppose that this disease is now more common in this country as the result of immigration from countries in which it is endemic, the clinical manifestations are still uncommon, or at any rate, seldom recognized. Treatment, on the whole, is disappointing. In early cases good results may follow the use of a sulphonamide such as sulphadiazine, in dosage of 5 g. daily for five to seven days. Considerable claims were made for the tetracycline drugs but their value seems to be limited. It has been suggested that their main effect may be on secondary infection, because they seem to be more effective in the late than in the early stages of the disease. Nevertheless, Henley (1953) obtained good

results in early cases of lymphogranuloma venereum with oxytetracycline by mouth in doses of 1 g. every six hours for about seven days. Erskine (1958) used chlortetracycline or oxytetracycline in dosage of 20 g. in ten days. With a single course of treatment the results were poor, but when he adopted the routine of giving a second course of oxytetracycline after an interval of seven days the response was satisfactory. Results with chloramphenicol by mouth have been disappointing, but Wood and his co-workers (1954) obtained good results by giving intramuscular injections of chloramphenicol. They gave doses of 4 g. at intervals of two or three days to a total of 12 g. In a recent report (Loughlin *et al.*, 1958-59) good results were claimed in the treatment of early cases of lymphogranuloma venereum with triacetyloleandomycin by mouth in dosage of 1 g. twice daily for five days.

GRANULOMA INGUINALE

Sporadic cases of this condition are now found in this country, usually in immigrants from the West Indies or Africa. Streptomycin by injection is effective in dosage of 4 g. daily given in divided doses over five days. Chloramphenicol, chlortetracycline and oxytetracycline are effective by mouth in dosage of 2 g. daily for ten to twenty days. Wood and his co-workers (1954) gave intramuscular injections, each of 4 g. of chloramphenicol, at intervals of two or three days to a total of 12 to 16 g., with healing in an average time of thirteen days in all but one of 24 cases. Claims have also been made for carbomycin by mouth (Whitaker *et al.*, 1953) in total dosage of 12 to 28 g. It was also effective when given intravenously in single daily injections of 500 mg. to a total of 14 to 20 g. Erythromycin is also said to be effective (Cordice *et al.*, 1953-54). Relapse is common with all forms of treatment but the relapsing condition responds in most cases to further treatment with the same or another antibiotic.

'NON-SPECIFIC' URETHRITIS

This common condition, of which the cause is unknown, is second in incidence only to gonorrhœa among the venereal diseases. In its complicated form it may have widespread effects especially involving joints. So-called Reiter's disease appears to be a manifestation of this condition. 'Non-specific' urethritis responds only fairly well to treatment and there is a considerable liability to infectious latency and relapse. The combination of streptomycin, 1 g. intramuscularly, with sulphathiazole, 5 or 6 g. daily by mouth, for five days gives fairly good results in some cases. Similar results may be obtained by combining the same dose of streptomycin intramuscularly with sulphamethoxypyridazine by mouth: 1 or 1.5 g. on the first day and then 0.5 g. daily for five days. The lower dosage required with this long-acting sulphonamide causes less discomfort to the patient. Oxytetracycline and tetracycline by mouth seem to be the most effective remedies. Clarke and his colleagues

(1955) and Merlin and Clarke (1956) obtained good results with tetracycline, 250 mg. four times daily for five days. Willcox (1955) obtained fairly good results with erythromycin, 6 g. in five days. The results were better than those obtained with 2.4 g. in six days. Spiramycin is also known to be effective, the usual dosage being 2 to 3 g. daily and the duration of treatment five days. Oates (1958) used a combination of two antibiotics, tetracycline and oleandomycin, in the treatment of a small number of cases, with good results. Results seemed to be equally good with dosage of 500 or 250 mg. six-hourly for five days.

If Reiter's disease develops, the patient requires admission to hospital, where he should remain until the active phase has passed. None of the antibiotics at present available influences the course of the arthritis, but tetracycline, 250 mg., should be given every six hours for five days, since it does appear to have a favourable influence on the urogenital infection in many cases. Strict bed rest, good nursing and good feeding are essential, and these measures combined with calcium aspirin for the relief of pain may suffice for the mild case. In more severe cases phenylbutazone, 200 mg. given twice or three times daily, is often strikingly effective.

There can be no hard and fast rules in the choice of the patient who should receive the steroid hormones. In general it will fall on one with florid disease, severe pain, wasting, fever, and an increasing erythrocyte sedimentation rate, who is failing to respond to the measures already outlined. The general principles governing the administration of these drugs obtain and usually the initial dose will be in the region of 60 mg. daily of prednisone or its equivalent, and a daily maintenance dose will be in the region of 20 mg. The patient whose disease is mainly confined to the knee-joints will sometimes benefit from aspiration of synovial fluid and injection of hydrocortisone, a procedure which may be repeated if necessary. If keratoderma blenorrhagica and circinate balanitis are present, the most that is usually required is the institution of simple hygienic measures to prevent secondary infection from occurring in moist areas. Conjunctivitis is usually mild and does not generally require treatment, but anterior uveitis, which may recur long after other manifestations of the disease, requires skilled management by an ophthalmologist along the lines suggested for iridocyclitis associated with gonorrhœa. When the active phase of Reiter's disease is subsiding, the patient should be mobilized and gentle active physiotherapy should be started.

CONCLUSION

New remedies have made the treatment of the venereal diseases safer and more satisfactory, but the fundamental problems are unchanged. The psychological stress which the diseases provoke and the dangers and disruption of family life which may result are still problems which loom large. The control of these diseases in the field of public health is unlikely to be

achieved with the introduction of new remedies alone, as the recent rise in the incidence of gonorrhœa and non-specific urethritis has shown. The ultimate control of this problem depends upon the control of promiscuity and lies outside the field of Medicine. On behalf of the individual patient, it should be remembered that the indiscriminate use of potent remedies may do untold harm. 'Diagnosis before treatment' is the golden rule.

References

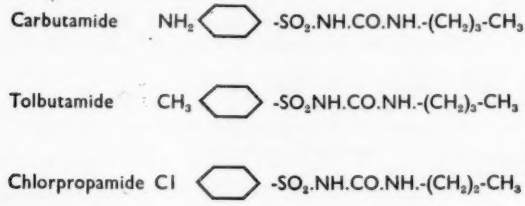
Alergant, C. D. (1958): *Brit. J. vener. Dis.*, **34**, 36.
Ashworth, A. N. (1958): *Ibid.*, **34**, 83.
Baler, G. R. (1956): *Arch. Derm. Syph. (Chicago)*, **73**, 489.
Barrett, C. D., and Burton, M. E. (1953): *Amer. J. Syph.*, **37**, 165.
Brett, R. (1953): *Derm. Wschr.*, **128**, 1141.
Butler, P. G., Brewer, A. F., Condit, P. K., and Johnston, J. (1952): *Amer. J. Syph.*, **36**, 269.
Clarke, B. G., Chaimson, H., Golden, H., and Tashian, H. N. (1955): *Bull. Tufts—New Engl. med. Cent.*, **1**, 34.
Cordice, J. W. V., Jr., Avecilla, M., Marmell, M., Shidlovsky, B. A., and Prigot, A. (1953-54): *Antibiot. Ann.*, p. 480.
Cradock-Watson, J. E., Shooter, R. A., and Nicol, C. S. (1958): *Brit. med. J.*, **i**, 1091.
Curtis, F. R., and Wilkinson, A. E. (1958): *Brit. J. vener. Dis.*, **34**, 70.
Deacon, W. E., Olansky, S., Albritton, D. C., and Kaplan, W. (1956): *Antibiot. Med.*, **2**, 143.
Erskine, D. (1958): *Brit. J. vener. Dis.*, **34**, 163.
Henley, K. S. (1953): *Ibid.*, **29**, 36.
Irgang, S., and Alexander, E. R. (1953): *Amer. J. Syph.*, **37**, 247.
King, A. J. (1956): *The Practitioner*, **177**, 471.
—— (1958): *Lancet*, **i**, 651.
Loughlin, E. H., Alcindor, L., and Mullin, W. G. (1958-59): *Antibiot. Ann.*, p. 333.
Merlin, H. E., and Clarke, B. G. (1956): *New Engl. J. Med.*, **255**, 663.
Metzger, W. I., Marmell, M., and Prigot, A. (1954): *Amer. J. Syph.*, **38**, 480.
Ministry of Health (1958): 'Report on the State of the Public Health for the Year 1957: Part II', H.M. Stationery Office, London, p. 67, 280.
Minno, A. M., and Davis, G. M. (1957): *J. Amer. med. Ass.*, **165**, 222.
Moore, J. E. (1951): *Lancet*, **i**, 699.
—— (1956): *Brit. J. vener. Dis.*, **32**, 217.
Oates, J. K. (1958): *Ibid.*, **34**, 38.
Perkins, H. A., Koch, R. A., Gara, G., Stephens, W. R., and David, W. D. (1955): *Antibiot. Med.*, **1**, 504.
Robinson, H. M., and Robinson, H. M., Jr. (1951): *Amer. J. Syph.*, **35**, 479.
Rodriquez, J., Weinstein, S., and Parkhurst, G. E. (1952): *Arch. Derm. Syph. (Chicago)*, **66**, 59.
Sheil, L. P. (1956): *Brit. J. vener. Dis.*, **32**, 251.
Smith, V. M. (1957): *New Engl. J. Med.*, **257**, 447.
Turner, T. B., and Schaeffer, K. (1954): *Amer. J. Syph.*, **38**, 81.
Whitaker, J. C., Prigot, A., Marmell, M., and Morgan, E. G. (1953): *Ibid.*, **37**, 466.
Willcox, R. R. (1955): *Antibiot. Med.*, **1**, 139.
—— (1956): *Brit. J. vener. Dis.*, **32**, 117.
—— (1958): *Ibid.*, **34**, 118.
Wood, C. E., Olansky, S., and Edmundson, W. F. (1954): *Arch. Derm. Syph. (Chicago)*, **70**, 625.
Zimmerman, M. C. (1957-58): *Antibiot. Ann.*, p. 312.

ADVANCES IN THE TREATMENT OF DIABETES MELLITUS

By WILFRID OAKLEY, M.D., F.R.C.P.

Physician in Charge, Diabetic Department, King's College Hospital

THE most important advance in the treatment of diabetes mellitus in recent years has been the introduction of the oral hypoglycæmic agents. In 1942, while investigating the chemotherapeutic action of the sulphonamide preparation, I.P.T.D., Jambon and his colleagues (1942) observed that it caused hypoglycæmia. The mechanism of this action was studied by Loubatières (1955), but he made no attempt to apply it to the treatment of diabetes. In the same year Franke and Fuchs (1955) recognized the hypoglycæmic action of the related compound, N-(p-amino-benzine sulphonyl)-N_2-butylurea, or carbutamide. Since the discovery of carbutamide several new hypoglycæmic sulphonamide derivatives have been produced of which the two most important are tolbutamide and chlorpropamide:—



PHARMACOLOGY OF ORAL HYPOGLYCÆMIC AGENTS

These drugs, when given by mouth, will lower the blood sugar in non-diabetic subjects, and in a certain proportion of diabetics, but the mechanism of this hypoglycæmic response is not yet fully understood; in this connexion it is worth while remembering that the same may be said of insulin. It is generally agreed that they lower the blood sugar only if the patient's pancreas is capable of secreting some insulin and, for this and other reasons, Loubatières (1957) put forward the view that they increase the output of insulin by the pancreas. The action of these drugs does not, however, appear to be identical with that of exogenous insulin in as much as they seem to have no direct effect on the utilization of carbohydrate by the peripheral tissues. There is also some evidence suggesting that they influence the enzyme systems of the liver and thereby reduce the output of hepatic glucose, which is unaffected by exogenous insulin. In addition, it has been suggested that the hypoglycæmic action may be due in part to inhibition of some contra-insulin substance or substances such as insulinase (Mirsky *et al.*, 1956), glucagon, or adrenal and pituitary hormones, but there is no convincing experimental evidence to support this hypothesis.

INDICATIONS FOR ORAL HYPOGLYCÆMIC AGENTS

The great majority of severe, and the majority of moderately severe, diabetics fail to respond to oral agents. This means that it is not only a waste of time, but may be dangerous, to use them in the treatment of any diabetic who, without insulin, is liable to develop significant ketosis. The type of diabetic who may be expected to respond well is the relatively mild, usually middle-aged or old, often obese and aketotic patient, whose disease can either be controlled by strict diet alone or with the addition of a small dose of insulin. Not all so-called suitable cases respond to the preparations at present available, the reason for failure being unknown. As with insulin, obesity should generally be regarded as a contraindication to the use of oral preparations, the correct treatment being weight reduction by means of a restricted carbohydrate low-calorie diet. The use of oral agents should therefore be restricted to those mild or relatively mild diabetics in whom:—

(1) Diet alone fails to bring the blood sugar within or near to the normal range.

(2) The dietary restriction required to control the diabetes causes progressive loss of weight or severe hunger.

(3) The withdrawal of insulin is not followed by relapse into significant ketosis; the dose of insulin that can be replaced is usually not more than about 30 units.

In addition to these general indications there may be some special reason for wishing to take a patient off insulin, such as blindness or the danger of nocturnal hypoglycæmia in elderly patients living alone. The mild diabetes which is sometimes produced by prolonged steroid therapy can be controlled by oral agents.

CARBUTAMIDE

This, the first of the oral hypoglycæmic agents to be used extensively, has now been given up on account of a number of serious and some fatal toxic reactions. Owing to its slow rate of excretion satisfactory blood levels were obtained with a single daily dose of about 1 g. Toxic reactions included sulphonamide sensitivity reactions with rashes and widespread arterial damage; some degree of thrombocytopenia was not uncommon and a few instances of agranulocytosis were recorded.

TOLBUTAMIDE

Now the most generally used preparation, tolbutamide differs from carbutamide in having no antibacterial and less toxic action; it also has a quicker rate of excretion and must therefore be given in divided doses, usually twice a day (Baird and Duncan, 1957). Side-effects are uncommon and include malaise, digestive disturbances such as anorexia and epigastric discomfort sometimes amounting to pain, and rashes which may be irritating. Blood dyscrasias are very rare and routine blood examinations are therefore not necessary. The standard tablet contains 0.5 g. of tolbutamide. Having first put the patient on a diet containing 100 to 150 g. of carbo-

hydrate, a convenient method of starting treatment is to give 1 g. (2 tablets) before breakfast and the evening meal for one week; if urine tests are negative and the blood-sugar level is satisfactory at the end of this period, the dose should be reduced to 0.5 g. (1 tablet) twice daily and tests repeated after a further week. Most patients will require at least 0.5 g. twice daily and some a total dose of 2 g. or, as a maximum, 3 g. daily. A few, however, may be controlled by 0.5 g. once a day before breakfast. In a small minority of cases the response to tolbutamide may be delayed, and it is therefore wise to continue treatment for at least two weeks.

CHLORPROPAMIDE

This recent addition to the available oral hypoglycæmic agents resembles carbutamide in its slow excretion and prolonged action, and need therefore be given only once a day. It is more effective than tolbutamide, but acts only in the same type of case. Patients who have relapsed on tolbutamide may respond to chlorpropamide. It is available in scored tablets of 250 mg. and 100 mg., and the maximum dose in any period of 24 hours should not exceed 500 mg. In practice it is wise, in my opinion, not to exceed 250 mg., which should be given before breakfast. This dose rarely produces toxic symptoms and, if the response is satisfactory, may be reduced to 200 mg. or 100 mg. daily.

Toxic effects of chlorpropamide include gastro-intestinal disturbances similar to those produced by tolbutamide, transient reversible leucopenia, eosinophilia and lymphocytosis, drug rashes and intolerance to alcohol. Impairment of liver function has been described, and may be associated with rashes and a raised alkaline phosphatase; it is only seen in association with the use of large doses of 500 mg. or more, and has been reported in about 1 per cent. of a small series of cases. After recovery the patient can be replaced on a small dose of the drug without apparent effect on the liver. Chlorpropamide may cause symptoms of hypoglycæmia, but they are not common, and are usually less severe than those produced by insulin.

When good diabetic control is maintained with small daily doses of tolbutamide (0.5 g.) or chlorpropamide (100 mg.) it is wise temporarily to discontinue their use to make sure that they are really necessary. The appearance of persistent ketonuria in any patient receiving oral hypoglycæmic agents should be regarded as an indication to stop this form of treatment and give insulin. The change-over from insulin to oral therapy should only be attempted in those patients in whom the withdrawal of insulin is not followed by ketonuria. It is usually, but not always, possible to recognize the patients who are likely to be suitable and, as a rule, their daily insulin requirement does not exceed about 30 units. There are several ways of making this change, but a simple one, recommended by Nabarro (1959), is to reduce the dose of insulin over a period of days and, when hyperglycæmia or glycosuria is observed, to start tolbutamide 0.5 g. three times, or chlorpropamide 250 mg. once, daily. This method has the advan-

tage not only of reducing the risk of serious relapse, but also of eliminating those cases which require neither insulin nor oral therapy. During the period of change-over and for at least a week after insulin has been stopped, the urine should be tested daily for sugar and ketone bodies; if the latter are found to be present oral therapy should be discontinued, and the patient at once put back on insulin. If the necessary facilities for urine and blood examination are not available the patient should be admitted to hospital.

Regular urine testing and supervision by practitioner or diabetic clinic are important in all patients receiving oral preparations as, apart from the possibility of toxic effects, a small number of patients develop resistance to their hypoglycæmic action with consequent relapse of their diabetes.

PHENETHYLDIGUANIDE

This oral hypoglycæmic agent is unrelated to the sulphonamide derivatives; chemically it more closely resembles synthalin. Its action does not appear to depend upon the presence of insulin, the reduction in blood sugar being effected by an increase in anaerobic glycolysis. Owing to the high incidence of gastro-intestinal side-effects, particularly nausea, it has so far received little trial in this country, but has aroused considerable interest in the United States. It is probable that new diguanides will be produced with less toxic action, but the danger of long-term therapy producing serious liver damage will have to be considered very carefully before they can be accepted as an alternative to insulin.

Whilst the oral agents constitute the greatest single recent advance in the treatment of diabetes, some progress has been made in the management of such complications as pregnancy, peripheral arterial disease, and neuropathy.

PREGNANCY AND DIABETES

There is increasing evidence that the most important factors in reducing fœtal loss are control of the maternal diabetes and bed rest for the month preceding delivery. The excellent results obtained by Priscilla White (1947), and attributed by her to hormone therapy, have been equalled by Pedersen (Brandstrup, Jörgensen and Pedersen, 1954) in Copenhagen without the use of hormones, the common factors in the management of their pregnant diabetics being control of the maternal diabetes and bed rest for the last month of pregnancy. Every effort must be made to keep the maternal blood-sugar level as nearly within normal limits as is compatible with absence of hypoglycæmia; at King's College Hospital we aim at a maximum upper level of 180 mg. per cent. during the last six or eight weeks. In order to achieve this degree of control it is essential to have the patient in hospital; this provides the added advantage of controlled bed rest and the opportunity to induce labour, or do a Cæsarean section, at short notice should the necessity arise. In this way it has proved possible to reduce fœtal mortality to about 15 per cent.

PERIPHERAL ARTERIAL DISEASE

The recognition of the important part played by neuropathy in the etiology of lesions of the feet has placed the treatment of this complication on a more logical basis. Lesions may be due to sepsis, neuropathy, ischæmia or a combination of these causes (Oakley *et al.*, 1956) and treatment varies accordingly. Uncomplicated sepsis should be treated in the conventional manner with adequate drainage. In the neuropathic case the lesion results from trauma of a desensitized foot, often in the form of pressure from ill-fitting shoes or from the unrecognized heat of a fire or hot-water bottle. In the absence of ischæmic changes treatment should be as conservative as possible with emphasis on the avoidance of pressure. When complicated by sepsis good results may be obtained by local operations designed to promote free drainage and the removal of infected tissue, especially bone. The neuropathic foot may present with gangrene of one or more toes, but this is due to localized arterial thrombosis and must be distinguished from the gangrene of generalized arterial disease affecting the whole of the foot or feet. Ischæmic lesions usually call for more radical surgery but, even in cases of extensive gangrene, below-knee amputation without suture gives excellent results (Silbert, 1944). Amputation above the knee is, or should be, an operation of the past in the vast majority of cases of diabetic gangrene.

NEUROPATHY

The treatment of this common complication has always been difficult, and it is doubtful whether any form of treatment, other than good diabetic control, greatly contributes to recovery. Recently we have been giving vitamin B complex intravenously, in the form of 'parentrovite', in doses of 10 ml. twice weekly for four to six weeks and have been impressed by the results, both in respect of relief of pain and rate of recovery. Even so it is usually many months before such recovery is anything like complete.

For two of the most serious complications, retinopathy and nephropathy, no effective remedy has yet been found. Hypophysectomy and bilateral adrenalectomy have been tried, but the results do not justify the risks involved or the disability that these operations may produce.

References

Baird, J. D., and Duncan, L. J. P. (1957): *Scot. med. J.*, **2**, 341.
Brandstrup, E., Jörgensen, G., and Pedersen, J. (1954): *Dan. med. Bull.*, **1**, 125.
Franke, H., and Fuchs, J. (1955): *Dtsch. med. Wschr.*, **80**, 1449.
Jambon, M., Chaptal, J., Vedel, A., and Schaap, J. (1942): *Montpellier méd.*, **21/22**, 441.
Loubatières, A. (1955): *Presse méd.*, **63**, 1701.
—— (1957): *Diabetes*, **6**, 408.
Mirsky, I. A., Perisutti, G., and Diengott, D. (1956): *Metabolism*, **5**, 156.
Nabarro, J. D. N. (1959): *Brit. med. J.*, **i**, 1466.
Oakley, W. G., Catterall, R. C. G., and Martin, M. M. (1956): *Ibid.*, **ii**, 953.
Silbert, S. (1944): *Amer. J. dig. Dis.*, **11**, 394.
White, Priscilla (1947): *Penn. med. J.*, **50**, 705.

ADVANCES IN THE TREATMENT OF LEPROSY

By R. G. COCHRANE, M.D., F.R.C.P., D.T.M. & H.

Adviser in Leprosy to the Ministry of Health; Technical Medical Adviser to the American Leprosy Missions, Inc.

It is now sixteen years since Faget and his colleagues first reported successful results in the treatment of leprosy by the use of a di-substituted derivative of diaminodiphenylsulphone—'promin'. The parent substance, now known as dapsone or DDS, was first synthesized in 1908 as a by-product in the production of aniline dyes. Interest was aroused again in the subject when Trefouël showed it to be several times more active than the sulphonamides against hæmolytic streptococci; and, in 1940, Rist, Floch and Harman showed that the drug gave some protection to rabbits infected with avian tuberculosis. But, as Bushby has pointed out, the assumption in those days was that the dose and concentration of DDS attained in the blood should be of the same order as that of the sulphonamides and such doses proved to be too toxic. Attempts were then made to produce less toxic derivatives and 'promin' was one of the first of these derivatives to be synthesized. In 1941, Feldman, Hinshaw and Moses reported successful results in the treatment of tuberculosis in animals with this drug. It was therefore a short step from here to try it in leprosy.

As the result of the use of di-substituted derivatives of the parent sulphone, leprosy came into the realm of treatable and 'curable' diseases, and there was ushered in a new era in the fight against this obstinate mycobacterial invader of the human tissues. It was not, however, until workers in Madras administered the parent sulphone parenterally, and Lowe demonstrated the possibility of giving the drug by the oral route, that this therapy for leprosy could be universally applied. In spite of the great and outstanding advances in the chemotherapy of leprosy, it is well to bear in mind a statement made some eight years ago: 'It would be a retrograde step if old slogans of twenty-five or more years ago were revived. Caution should still be the watchword in relation to statements concerning the absolute success of modern therapy in leprosy'.

THE IMMUNOLOGICAL APPROACH

It does not come within the scope of this article to recapitulate the enormous amount of work which bacteriologists and other research workers have done in their attempts to grow the *M. lepræ* on artificial media. It is, however, of the utmost importance to discover an animal which can be infected with *M. lepræ* so that our therapeutic approach to the disease can be more logical, and more likely to be successful. Mention might be made,

in this connexion, of the recent work of Chatterjee (1958) in relation to hybrid mice, to Gunders' work (1959) on chimpanzees, and to the investigations of Chapman Binford, who worked along the generally noted observation that *M. lepræ* prefer anatomical sites relatively low in temperature. These workers have succeeded in producing multiplication of *M. lepræ* in the histiocytes of the reticulo-endothelial system of these animals, which may be of great value in therapeutic investigations.

These experiments have also a direct value in relation to the question of immunology, for it appears from this and other work, particularly that of Hanks and, more recently, Robson, that an understanding of the immunological approach to leprosy would be of great value, and possibly hasten the day when we can apply standard remedies for the treatment of leprosy without experiencing relapses, and without a significant number of cases remaining positive, even after seven years, or more. In this connexion it is of interest to note that certain workers, particularly Kuper (1958), have recently stressed that BCG vaccination may be an additional method of treatment. According to Kuper, BCG vaccination apparently stimulates lymphatic production and this—admittedly on limited evidence—is said to be a favourable factor in hastening recovery.

SPECIFIC THERAPY

Sulphones.—It is universally accepted that the routine treatment of leprosy should be by means of the parent sulphone or one of its derivatives. That recommended is a 50 per cent. aqueous solution of solapsone, parenterally. A great deal of work has been done during the last decade with regard to the minimum effective oral dose of diaminodiphenylsulphone (dapsone; DDS) and its derivatives (Cochrane, 1959). It is now generally considered that the former high dosage of DDS (200 to 300 mg. a day) is unnecessary and is conducive to the precipitation not only of toxic signs but of reactions. Generally speaking, practitioners will find that the most practical method of treatment of leprosy is by the oral use of DDS, and the points which must be stressed are that the initial dose must be small (25 mg. twice a week), and the increase must be gradual, going up to a maximum of 300 mg. twice a week. Under the standard methods of treatment most patients will respond satisfactorily.

Diphenyl thiourea.—When the progress of a case under treatment with DDS is not satisfactory, there are now other remedies available. One which has now been more thoroughly tried than any of these is the diphenyl thiourea derivative, 'CIBA 1906' (DPT) which has recently been given the official name of Thiambutosine. Davey (1959) and Davey and Hogerzeil (1959) have shown that it is comparable in its effectiveness to DDS and less reaction producing. The optimum dosage advocated is 2 g. daily, starting with 250 mg. (half a tablet) a day, and increasing every fortnight by half a tablet until a maximum of 2 g. a day is reached. Further, Davey has shown that there is a tendency for drug

resistance to develop after a period of about four years. It therefore appears to be inadvisable to use DPT in such cases for a longer period than two to three years. By changing over to this drug, however, cases which are difficult to treat, or show intolerance to DDS or one of its derivatives, may gradually become stabilized, and, as is often the case, it may be possible to switch the patient back to DDS after a course of DPT has been completed. The starting dose of DDS should then be 25 mg. (quarter of a tablet) twice a week, increasing by 25 mg. every fortnight until 100 mg. is reached. After this the increments are monthly at the rate of 100 mg. a month until 300 mg. twice a week is reached.

Ditophal.—At the recent International Congress of Leprosy held in Tokyo, Davey reported the treatment of leprosy by inunction with a new preparation known as ditophal ('etisul'). This is a most interesting drug and is a derivative of ethyl mercaptan. In the form of a cream, it is absorbed rapidly by the skin, and evidently forms a complicated compound with the lipids of the tissues. Preliminary results suggest that ditophal has an action on the *M. lepræ* far greater than any other drug yet discovered. Within a relatively few months, however, according to Davey, resistance forms appear, and therefore 'etisul' alone may not provide the complete answer to the therapy of leprosy. Davey has further suggested, and has supplied evidence of the fact, that if 'etisul' is combined with DDS and DPT thiourea resistance is far less likely to develop. Such an approach to the therapy of leprosy is logical and is along lines similar to those advocated in the therapy of tuberculosis. The one handicap in the treatment of leprosy by inunctions of ditophal is that the drug has a very strong odour which is objected to by many patients. If, however, the patient takes a shower or a bath after the drug has been rubbed in and no clothes are put on until the patient has washed, the objectionable garlic odour is considerably reduced.

Therapeutic trials with ditophal have been largely undertaken on African patients and, as yet, it has not had an extensive trial on patients of the Caucasian race. It is a well-known observation that leprosy in the Caucasian and Mongolian races is a much more serious disease than in the African or Indian, and that lepromatous leprosy in these groups is much more difficult to treat, for these patients more often show severe forms of erythema nodosum. Further trials with this drug in these cases will be awaited with considerable interest.

The therapy of leprosy is apparently passing through a similar phase to that seen in tuberculosis, and recently it has been stated with reference to tuberculosis that 'it is now possible to aim at a 100 per cent. success in the treatment of pulmonary tuberculosis caused by organisms sensitive to the standard drugs'. It is therefore hoped that by the development of a three-pronged attack such a satisfactory state of affairs may at last be reached in the treatment of leprosy, even though by adopting such methods it will complicate therapy considerably and, in many instances, will involve the return to more direct institutional treatment. The advances that have been

made in the treatment of leprosy during the past decade have been very considerable, and it can be hoped that within the foreseeable future doubts and questions with regard to the permanent efficacy of treatment in lepromatous cases will be finally banished. It can be said, in summary, that we now have drugs in our armamentarium against leprosy which will enable the majority of cases to overcome the infection and reach a stage of 'clinical cure'. There is, however, still a hard core of cases which do not seem to respond adequately to the newer methods of treatment: either because of reactions due to tissue hypersensitivity or because of reactions resulting from the circulation of the breakdown products of the mycobacteria in the tissue, and it may be well to turn now to a discussion of this subject.

TREATMENT OF REACTIVE STATES IN LEPROSY

In the tuberculoid type of leprosy, or that variety of the disease which presents both tuberculoid and lepromatous features known as dimorphous or borderline leprosy, a state of active and acute tissue response is liable to arise due to a process of hypersensitivity. It cannot be too strongly emphasized that when such cases pass into reaction all treatment should stop. For those who are not familiar with the detailed classification of the disease, it may be said that, wherever there are several large lesions or multiple lesions, whether they be symmetrical or asymmetrical, which show themselves in plaques and which become erythematous, angry-looking and desquamate, treatment must be stopped at once and measures be undertaken to reduce to a minimum the damage caused by the inflammatory reaction. Steroid therapy has been advocated for these intense tissue reactions but, generally speaking, this is not advised, for, if corticosteroids are used, very massive doses will be required—in the region of three or four hundred milligrams a day of cortisone or a hundred milligrams of prednisone—and, quite apart from the expense of the remedy, it is doubtful whether even this dosage would have an appreciable effect.

It is known, however, that in tuberculoid leprosy and in those cases known as dimorphous leprosy, particularly the atypical tuberculoid lesions, the acute reactive states tend to subside; the more acute the reaction, the quicker is the subsidence of the lesions. The general principle therefore remains: all treatment must be stopped and the inflammatory surfaces protected. Treatment should only be restarted after the acute signs of activity have ceased.

In passing, it must also be remembered that these forms of leprosy may be extremely mutilating and Brand has shown that by meticulous care and attention, and adequate physiotherapeutic measures, combined when necessary with operative surgery, a large amount of the deformity, which is the result of these reactive states, can be completely prevented.

REACTIONS IN LEPROMATOUS LEPROSY

This, in itself, is a subject which is too complicated to deal with in such a contribution as this. There is, however, one form of reaction with which

anyone who is dealing with leprosy must be familiar, known as *erythema nodosum leprosum*. This condition is seen in the eruption of subcutaneous, rose-spot nodules which are generally situated on the outer aspects of the extremities, particularly on the thighs, forearms and the face, but occasionally they may be seen all over the body, and sometimes in profusion. Individual lesions do not usually last for more than twenty-four to forty-eight hours, but occasionally may last as long as a week or ten days, leaving an area of desquamation. In milder attacks there is slight malaise but no fever. When the attack is more severe there may be headache and severe malaise, and a febrile condition, which shows itself in the form of an intermittent temperature rising to a peak between 16.00 and 18.00 hours. When the erythema nodosum is severe, and it is impossible to continue sulphone therapy without precipitating the reaction, the physician should seriously consider the use of the steroids. In such cases it is recommended that treatment be initiated with a low dosage: for example, 25 mg. of cortisone acetate, or 5 mg. of prednisolone daily, gradually increasing to that dosage which will cause the patient to be comfortable, not necessarily to suppress the erythema nodosum completely, but sufficiently for the specific treatment to be continued.

The general principle to bear in mind is that, once corticosteroids are given these must be continued for a sufficiently long time for the erythema nodosum phase to pass. If the erythema nodosum is severe the parent sulphone is contraindicated. It should certainly not be given by mouth, and I am of opinion that the drug which should be used is a 50 per cent. aqueous solution of solapsone. One can give as low a dosage as 0.1 ml. of a 50 per cent. aqueous solution of solapsone twice a week, and gradually increase the dosage until 0.5 ml. twice a week is reached. When this dose is reached, that of whatever corticosteroid is being used is gradually reduced until it is stopped altogether. The same dose of solapsone is continued for a period of three months, and the dosage is then increased slowly again by 0.1 ml. until 1 ml. twice a week is given intramuscularly or deep subcutaneously. It has been shown that 1 g. of solapsone (1 ml. twice a week) is an effective therapeutic dose. The patient should be continued on solapsone for at least a year before he is put on the parent sulphone again. Cortisone, prednisone and prednisolone are difficult to administer as outpatient treatment. It is therefore of interest to note that Miguel has recently shown that intramuscular injections of prednisolone given once a week will control erythema nodosum in many cases, and enable therapy to be continued.

EYE COMPLICATIONS

Cortisone is invaluable in eye complications in leprosy, particularly in iritis and iridocyclitis. Choyce recommends that 1 per cent. cortisone acetate drops be used three or four times a day, combined with atrophine either in the form of 1 per cent. ointment, or as drops. The main principle in the treatment of eye complications in leprosy is to suppress the inflammatory reaction

by the use of the steroids and maintain a maximum dilatation of the pupil. The knowledge acquired during the past ten years with reference to the treatment of ocular conditions in leprosy has been increased considerably, and it can now be said that no patient with leprosy, complicated by ocular signs, need go blind. Cortisone, combined with the judicious use of the specific remedies for leprosy, should avert blindness in the great majority of instances. The principles are dilatation of the pupils and suppression of inflammatory reaction by cortisone or one of the other corticosteroids.

CONCLUSION

It can be said that, as in tuberculosis so in leprosy, new chemotherapeutic discoveries have led not only to more successful treatment but have stimulated research workers (e.g. Weddell *et al.*, 1959). Today, leprosy is probably of more serious import as a world problem than such diseases as trypanosomiasis, onchocerciasis, and even plague, and it is not a problem from which we are immune in Great Britain. Indeed, it is now one of the diseases which the practitioner has to consider in the routine of his general practice, for there are over three hundred known cases of leprosy today in this country and the number may be as high as four hundred. On an average, two or three new cases are reported each month. It must also be remembered that in dermatological and neurological clinics cases of leprosy present themselves from time to time for diagnosis.

The new advances in the treatment and care of leprosy patients have now made it possible to say that leprosy has definitely entered into the realm of treatable diseases.

References

Chatterjee, K. R. (1958): *Leprosy Rev.*, **30,** 9.
Cochrane, R. G. (1959): 'Leprosy in Theory and Practice', Bristol.
Davey, T. F. (1959): *Leprosy Rev.*, **30,** 20.
——, and Hogerzeil, L. M. (1959): *Ibid.*, **30,** 61.
Faget, G. H., Pogge, R. C., Johansen, F. A., Dinan, J. F., Prejean, B. M., and Eccles, C. G. (1943): *Publ. Hlth Rep.* (*Wash.*), **71,** 999.
Feldman, W. H., Hinshaw, H. C., and Moses, H. E. (1941): *Amer. J. Path.*, **17,** 578.
Gunders, A. E. (1959): *J. trop. Med. Hyg.*, **61,** 228.
Kuper, S. W. A. (1958): *Leprosy Rev.*, **30,** 13.
Weddell, G., *et al.* (1959): In 'Leprosy in Theory and Practice', edited by R. G. Cochrane, Bristol, p. 96.

ADVANCES IN ANÆSTHESIA

By T. CECIL GRAY, M.D., F.F.A.R.C.S.
Professor of Anæsthesia, University of Liverpool

THIS review of progress in anæsthesia will include advances in clinical practice which have been made since the subject was last reviewed in 'Advances in Treatment' in 1956 (Wylie, 1956). It is indicative of the continuous growth of this subject that a review should be necessary so soon; yet most of the research of the last three years has been directed towards a better understanding of established practices, such as intermittent positive pressure pulmonary ventilation, or of the pharmacological action of drugs already widely used, such as, for example, the relaxants.

INTERMITTENT POSITIVE PRESSURE RESPIRATION

The interest of anæsthetists in pulmonary ventilation and their familiarity with its problems have resulted from the daily use of potent paralysing drugs. For some years 'intermittent positive pressure respiration' (I.P.P.R.) has been their daily chore. I.P.P.R. is carried out by the intermittent manual or mechanical inflation of the lungs with air, oxygen or an anæsthetic mixture. This manœuvre implies obviously a reversal of the normal intrapulmonary pressures and, to avoid circulatory depression, a specific ideal curve of inflation and deflation must be achieved. This ideal pressure curve is attained by rapid inflation to an intrapulmonary pressure of 15 to 20 cm. H_2O, rapid deflation to 0 cm. H_2O and a pause before the next inflation-deflation cycle begins. This pause must be at least equal in duration to the inflation-deflation phase. When the chest is closed it is advantageous to have the pressure during the expiratory pause lower than atmospheric (about -5 cm. H_2O) and so reduce the mean intrathoracic pressure. In this way the venous return is facilitated and there is some compensation for the loss of the 'respiratory pump' mechanism. This negative or sub-atmospheric phase is essential in patients suffering from hypovolæmic shock; otherwise further circulatory collapse always follows the institution of I.P.P.R. (For a review of recent work on this aspect of pulmonary ventilation see Dobkin, 1958.) Various mechanical respirators have been devised to provide ideal pressure and inflation characteristics. Some have the advantage of permitting the patient to initiate the inspiratory phase by his own inspiratory efforts—triggering—thus permitting them to be used to assist a patient who has some spontaneous but inadequate respiration. (For details of all the current machines see Mushin *et al.*, 1959.)

Attention was acutely focused on the possible therapeutic applications of I.P.P.R. by the work of Lassen and his colleagues (Lassen, 1953) during the Danish epidemic of poliomyelitis in 1952. Since then this technique has been found life-saving in many medical conditions.

Myasthenia gravis.—The interest of anæsthetists in this condition and their familiarity with its problems also spring from their daily employment of potent drugs acting at the myoneural junction and their antagonists. The respiratory crisis of this disease seems to be becoming more common.

Griffin and his colleagues (1956) described a case in which there was inadequate respiratory activity for forty-four days. In this patient the employment of intermittent positive pressure respiration provided by a mechanical respirator permitted the withdrawal of all anticholinesterase drugs: for it was considered that overdose with these might be prolonging the crisis. Thymectomy was performed on the thirty-seventh day of this period of apnœa and the patient subsequently made a good recovery.

Churchill-Davidson and Richardson (1957) have suggested that prolonging the depolarizing activity of acetylcholine by the use of anticholinesterase substances may produce a condition of fatigue at the endplate. Rest of the endplate and a reversal of this condition may in some cases result from the administration of an anti-depolarizing drug such as *d*-tubocurarine. They described a case which was treated in this way and respiratory paralysis maintained with tubocurarine for eight days.

The patient was kept sedated and his lungs ventilated with a Beaver respirator through a tube in a tracheostomy—which also permitted frequent and effectual bronchial aspiration. There was, of course, full attention to nutrition, fluid and electrolyte balance. This treatment resulted in remarkable improvement and ultimately recovery from the immediate crisis, although the patient died during the night some weeks later, apparently due to acute respiratory failure.

Most van Spijk and Lammers (1957) have described similar cases, but point out that relief is not constant when this procedure is adopted and that, in any case, this is a disease subject to remissions. Further evidence must be awaited before any conclusion can be arrived at, but this is a treatment which is attractive at least on theoretical grounds.

Other conditions.—The part that can be played by anæsthetists and their techniques in the treatment of tetanus is well known (Ablett, 1956), but their special skill in pulmonary ventilation and long-term sedation has been employed recently in a wider range of diseases. A good example is given by the treatment of a case of salicylate poisoning (Freier *et al.*, 1957) in which the tachypnœa, respiratory alkalosis and hyperthermia were treated by the induction of complete paralysis with a curare-like drug and the use of intermittent positive pressure respiration. The convulsions associated with status epilepticus (Nisbet, 1959) and with oliguria in children (Nisbet and Wilson, 1959) have also been treated in this way. Intermittent positive pressure respiration with tracheal and bronchial aspiration is also being employed to tide the chronic bronchitic and emphysematous patient over the crisis of acute respiratory failure.

In all these conditions tracheotomy has become usual. This operation facilitates the artificial pulmonary ventilation by removing the necessity for prolonged use of an endotracheal tube. The larynx is less able to tolerate a tube for long periods than the trachea. Tracheotomy also reduces the

respiratory dead space and provides ready access to the tracheo-bronchial tree for the frequent aspiration of secretions which is always necessary.

HALOTHANE

Wylie, in the closing paragraph of his 1956 review, stated that 'much research has been carried out recently in an endeavour to produce an all-purpose, but safe, non-explosive inhalational anæsthetic—in fact the sort of drug which would possess the intrinsic advantages of ethyl ether'. Thirteen years ago, Robbins (1946) investigated the anæsthetic properties of several fluorinated hydrocarbons. In the search for more potent non-explosive anæsthetics, pharmaceutical chemists have turned again to this comparatively unexplored group of organic compounds. One of them, trifluoro-ethyl-vinyl-ether ($CF_3CH_2OCH = CH_2$) was investigated by Krantz and his colleagues in 1953 (Lu *et al.*, 1953; Krantz *et al.*, 1953) and reported on by, amongst others, Dundee and his colleagues (1957). This was a potent anæsthetic providing a rapid induction and recovery. Its disadvantages were depression of respiration, tachypnœa and indifferent muscle relaxation. Furthermore, it was explosive in anæsthetic concentrations. In 1956, however, Raventós described the pharmacology of a compound originally synthesized by Suckling in the laboratories of Imperial Chemical Industries Ltd. This substance, 'fluothane', with the chemical formula $CF_3CHClBr$, was later given the approved name of halothane.

Physical properties.—Halothane is a colourless liquid with an aromatic odour not greatly dissimilar to chloroform. It is unstable and must be stored in coloured bottles; thymol (to a concentration of 0.01 per cent.) is added, to increase its stability. Its boiling point is 50° C., its vapour is heavier than air and it is non-inflammable and non-explosive in air or oxygen. Halothane is only slightly soluble in water, less so than the other volatile anæsthetic agents, but it is extremely soluble in fats, having an oil/water solubility partition coefficient of 330, compared with 100 for chloroform. The result of this is that the induction of anæsthesia is rapid and the recovery from short periods of anæsthesia is prompt but, because of the high fat solubility, complete elimination of the drug takes a considerable time after longer administrations. Clinical experience has shown that, after prolonged narcosis with anything other than minimal concentrations of halothane, patients may remain asleep for hours (Burn *et al.*, 1957).

PHARMACOLOGICAL PROPERTIES OF HALOTHANE

In concentrations up to 2 per cent. it is easily inhaled and it causes little if any tracheo-bronchial irritation so that it provides a smooth and easy induction of anæsthesia. A striking feature in patients under its influence is the complete absence of appreciable mucus or salivary secretions in the mouth and air passages. The relaxation it provides is considered by some to be adequate for lower abdominal operations but it is insufficient for

procedures above the umbilicus. It is a potent respiratory depressant and, as the anæsthesia deepens, rapid respiratory rates and low tidal volumes are common.

The effects of halothane on the cardiovascular system have been the object of much research and debate. Clinically the invariable results of the administration of this substance are bradycardia and a fall in blood pressure, the severity of which is directly related to the depth of anæsthesia and it may be profound. The bradycardia is relieved by atropine, which should always be a constituent of the premedication if halothane is used. It is the significance of the fall in blood pressure which has given rise to debate. In his original article Raventós (1956) considered that the hypotension was due to a block of sympathetic impulses and he postulated that this agent had a marked effect, particularly on the mesenteric ganglia. Burn and his colleagues (1957) showed that in animal preparations halothane produced a degree of myocardial depression not far short of that produced by chloroform. They appeared to regard the hypotension as attributable to a central effect on the vasomotor centre and perhaps myocardial depression, and doubted whether ganglionic blockade played any part. Severinghouse and Cullen (1958) have emphasized the importance of myocardial depression as a cause of this hypotension, but this opinion has by no means received unanimous support and indeed has been contradicted by other workers (McGregor *et al.*, 1958; Wyant *et al.*, 1958). All anæsthetic agents are myocardial depressants and the intensity of this effect is directly related to their potency as anæsthetic agents and to the dose which is used. In a recent report Burn and Epstein (1959) have shown that halothane relaxes the smooth muscle of the intestine, blood vessels and spleen. Under its influence the spleen first constricts and then dilates. They suggest that this direct action on the vessels and spleen may play a part in the production of the hypotension. It seems likely that all the reasons which have been suggested for the hypotension during halothane anæsthesia are in fact valid, but that in ordinary clinical dosage myocardial depression is no more important than with any other anæsthetic.

As might be expected from such a highly halogenated compound, cardiac arrhythmias may occur but surprisingly they have not been found to be a serious hazard. The myocardium is sensitized to adrenaline (Raventós, 1956) and there have been reports of cardiac irregularities of a serious nature following the injection of adrenaline in man under the influence of halothane (Brindle, Gilbert and Millar, 1957). A finding, suggestive of a possible similarity to chloroform in this respect, is that intense stimuli under light halothane anæsthesia may give rise to cardiac arrhythmia (Robson and Sheridan, 1957).

There is no evidence that halothane produces any greater liver or kidney damage than other anæsthetic agents in common use, and another surprising finding has been the absence of hyperglycæmia following its administration (Stephen *et al.*, 1957).

ADMINISTRATION OF HALOTHANE

As it is such a potent anæsthetic, it is important that a reliable vaporizer should be used to enable accurate percentage mixtures to be administered. That designed by Cyprane Ltd.—the 'fluotec' vaporizer—is calibrated to deliver 0.5 per cent. to 3 per cent. halothane vapour when the gas flow through it ranges from 4 to 16 litres per minute. This vaporizer is temperature compensated and is adapted for use with the ordinary Boyle anæsthetic machine which may be calibrated to give adequately accurate mixtures (Mapleson, 1957). Marrett (1957) has described a method of administering halothane using the ether jar of the standard Marrett machine and a closed circuit with a gas flow of only 400 to 500 ml./min. The closed circuit, however, is better avoided by all except those with considerable experience of the administration of this drug, as there is a danger of build-up in concentration unless the gas flow into the closed circuit is kept high. This problem has been considered by Newman (1958) who, after a full study of all the factors involved, has suggested that 'constant inspiratory vapour concentrations may be obtained with vaporizers perfused by respirations and in the presence of total rebreathing, provided the vaporizer is set to have a low efficiency'. A rising concentration, in whatever system, is due to a rate of administration which is excessive for the particular circumstances. The advantages of the closed circuit with a drug as expensive as halothane are not negligible, and with care and judgment there is everything to be gained by those sufficiently experienced to use this technique. A warning is given by Brown and Woods (1958) that halothane may have a deleterious effect on the metal of closed-circuit vaporizers.

It is important to appreciate that *d*-tubocurarine chloride may be potentiated by halothane and if it or other relaxants are used, they should be given with care and in reduced dosage.

Induction and maintenance.—The premedication must always include atropine and some authorities recommend that the dose of atropine should in fact be larger than is usual. Anæsthesia may be induced with an intravenous barbiturate followed by a concentration of halothane working up to 2 to 3 per cent. A concentration of 0.5 to 1 per cent. will be found adequate for maintenance. Pulmonary ventilation must be kept adequate and a careful check maintained on the blood pressure. If the hypotension becomes profound and it is certain that other factors such as blood loss do not account for it, the treatment is to lighten the anæsthesia; some workers give a vasoconstrictor such as methoxamine, but this should seldom, if ever, be necessary.

Azeotropic mixture with ether.—An attempt was made to increase the safety of halothane, as well as its analgesic and relaxant properties, by investigating the properties of mixtures of it with ether. Hudon and his colleagues (1958) and Boivin and his colleagues (1958) have described a mixture distilling at a temperature of 51.5°C. giving a constant proportion of the two vapours. This azeotropic mixture contains 31.7 per cent. ether

and 68.3 per cent. halothane. It was found to be non-inflammable and was claimed to have a greater margin of safety and to give rise to fewer cardiovascular disturbances than halothane alone (Dobkin *et al.*, 1959). Raventós (Raventós and Dee, 1959), however, does not consider that this mixture differs appreciably in its pharmacological properties from the original compound, and points out that in concentrations above 3.5 per cent. it is, in fact, inflammable.

INDICATIONS FOR HALOTHANE

At the time of its introduction, halothane caused considerable interest because it seemed that here might be an approach to the ideal in anæsthesia. Potent and non-inflammable, causing little or no liver and renal toxæmia, it could provide quick induction and recovery. Its disadvantages, however, namely respiratory and cardiovascular disturbances and poor relaxation, soon made it clear that its use was limited. A striking clinical impression has been that patients appear remarkably fit after its administration and the claim has been made that halothane is especially indicated in patients in poor condition and with circulatory collapse (Pope, 1957; Johnstone, 1958). Many, however, are finding its most useful application to be that of a supplement to nitrous oxide/oxygen anæsthesia for procedures not requiring relaxation, and for this it is to some extent replacing the widely used trichloroethylene and cyclopropane. It has been suggested that this would be a useful adjuvant to nitrous oxide and oxygen even for minor procedures, particularly dental extractions in the chair (Walsh, 1958). The potency of this agent and the rapid recovery following its administration are claimed to be advantageous in these circumstances, and Goldman (1959) has described a special vaporizer which can be attached to the ordinary dental gas machine and which, it is claimed, at any gas flow will not give a vapour concentration of halothane greater than 2 per cent. Despite these advocates the circulatory and respiratory effects of the drug in all except minimal concentrations would seem to make it potentially dangerous for such work, and it should only be used in these circumstances by experienced anæsthetists.

Brown (1959) has drawn attention to its possible use for bronchoscopy in children. In this technique anæsthesia is induced by nitrous oxide and oxygen and halothane added when the child is asleep. Full surgical anæsthesia is obtained with 1.5 to 2 per cent. halothane, and topical anæsthesia is then achieved by spraying the larynx and cords with 4 per cent. lignocaine. During the bronchoscopy, halothane, 1.5 per cent., and oxygen are delivered to the patient through the oxygen tube on the Negus type bronchoscope.

HYPOTHERMIA

The use of hypothermia for cardiac and vascular surgery and neurosurgery has become well established and quite routine in many centres. This

procedure, however, should be limited to those circumstances in which a definite lowering of oxygen demand is required, for further evidence has been obtained that lowering the temperature probably does not protect the body from the effects of trauma (Macphee, Gray and Davis, 1958).

For cardiac surgery, except for the shortest procedures, attention has been directed more and more during the last three years towards the use

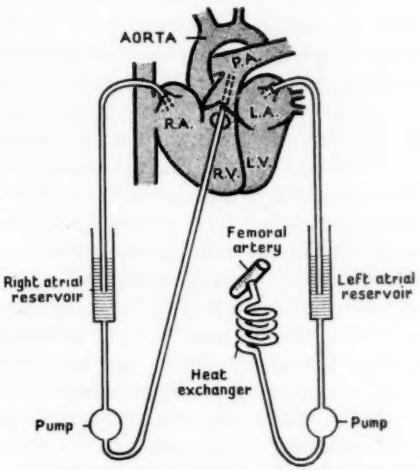


FIG. 1.—Diagram of experimental extracorporeal circuit (after Drew *et al.*, 1959, by courtesy of the authors and the *Lancet*).

of heart-lung machines, for hypothermia alone (body temperatures around 29°C.) permitted only ten minutes of circulatory arrest. With heart-lung machines periods of up to one hour of cardiac by-pass are possible. Recently, however, a great advance has been made by Drew and his colleagues (Drew *et al.*, 1959; Drew and Anderson, 1959) who have discovered a technique by which the body temperature of human patients may be lowered to around 15°C. Under this 'profound' hypothermia circulatory arrest can be permitted safely for up to forty-five minutes. These low temperatures are achieved by by-passing the heart and using the patient's lungs to oxygenate the blood during the cooling. The result is that an adequate circulation can still be maintained and cooling continued after the heart has failed.

The technique (fig. 1) consists of taking the blood through a catheter from the left atrium into a reservoir from which it is pumped to a heat exchanger and then back into the femoral artery. As the temperature is lowered and the heart begins to fail blood is drawn also from the right atrium similarly into a reservoir and pumped directly into the pulmonary artery via a catheter passed through a stab wound in the right ventricle. The general circulation is thus supplied with an adequate volume

of oxygenated blood to maintain a blood pressure near normal when the heart has failed.

The body temperature can be lowered to 13 to 15°C. within thirty to forty-five minutes. Rewarming is equally rapid.

This technique has opened up new possibilities to the cardiac surgeon. Its advantage over heart-lung pumps would seem to be that the patient's own lungs are used as an oxygenator, for the mechanical oxygenators are largely responsible for blood destruction when heart-lung machines are used. With this method, cooling is rapid and if very profound temperatures prove to be obtainable, periods of arrested circulation even longer than forty-five minutes may come to be permitted.

ANÆSTHESIA IN THE DENTAL CHAIR

Although over the last fifteen years there have been considerable changes in the technique of anæsthesia for major procedures, there has not been an equal rate of development in the techniques available for minor operations. Approximately three million anæsthetics are given in the dental chair every year in this country and, *faute de mieux*, the asphyxial type of anæsthetic is still not infrequently used. Bourne (1957) has emphasized the very real dangers of the hypoxia which often accompanies the administration of nitrous oxide in the dental chair, and has presented evidence for the possibility of a faint occurring during the induction or maintenance of anæsthesia. It is easy to understand how dangerous could be the combination of an even mild degree of hypoxia with the cerebral ischæmia resulting from such a faint. Fainting is most likely to occur in the upright position, which is that usually employed in the dental chair. Bourne stresses the importance of an early diagnosis of this condition by careful observation of the patient's colour and pulse. As soon as there is evidence of a fall in blood pressure, it becomes a matter of extreme urgency that the head should be lowered and the patient should be laid at least flat and, if possible, head down. Failure to do this may cause, if not death, severe and irreversible cerebral damage.

Various suggestions for avoiding hypoxia during dental anæsthesia have been made. Halton (1959) has repeatedly pointed to the advantages and safety of the rapid intravenous injection of a very small dose of barbiturate (not exceeding 75 mg. of thiopentone or its equivalent of other ultra-rapid barbiturates). Following this, anæsthesia can be maintained with nitrous oxide and full oxygenation, supplemented, if necessary, by minimal concentrations of trichloroethylene. A quick recovery of consciousness follows such a small dose of barbiturate injected rapidly. Tom (1956) has developed the suggestion of Klock (1955) that adequate analgesia and amnesia (a condition referred to as 'amnalgesia') can be obtained in most patients with nitrous oxide and 20 to 25 per cent. of oxygen, provided that the inhalation is continued for an adequate time. The use of halothane for dental surgery

has already been referred to, but this technique, like that suggested by Burton and Battersby (1958) in which thiopentone, a relaxant and endotracheal intubation is used, is better left to the specialist anæsthetist.

The fact is that a fully satisfactory method of anæsthesia for these short cases has not yet been discovered. That anxiety is felt on this score is evidenced by the institution by the Association of Anæsthetists of Great Britain and Ireland of a valuable prize for the best work directed towards this end.

IATROGENIC DISEASE

The influence of various diseases and pathological conditions on the action of drugs used by anæsthetists has been appreciated for some time. For example, myasthenics are known to be sensitive to non-depolarizing relaxants. Such conditions as anæmia, dystrophia myotonica, uræmia, liver disease and porphyria are known to effect the reaction of patients to intravenously injected barbiturates. Dundee (1958) has recently drawn attention to a group of medical treatments which may produce untoward reactions when the patients receiving them are anæsthetized. Thus, treatment with hypotensive and tranquillizing drugs may potentiate drugs given during anæsthesia. Caramiphen, used in the treatment of Parkinsonism, was found by Pulver (1955) to potentiate barbiturates given subsequently, and Dundee suggested that benzhexol may potentiate anæsthetic and relaxant agents.

By far the most important, however, of these therapeutic procedures which may influence anæsthesia is the administration of cortisone. Unimpaired functioning of the pituitary-adrenal axis is necessary for an adequate protective response to the stress of surgery and anæsthesia. Preoperative cortisone must, of course, be given to patients suffering from pituitary or adrenal insufficiency such as, for example, those with Addison's disease, Cushing's syndrome, or when the adrenals are being removed for the treatment of carcinoma. The administration of cortisone for other medical conditions, however, produces an inhibition of the natural secretion from the adrenal cortex which may last for many months after cessation of the therapy. If such patients are anæsthetized and operated upon they may show acute circulatory failure, which will respond only to the intravenous administration of hydrocortisone. When the patient has been on cortisone therapy at any time over the twelve months prior to a proposed operation, it is essential that they should receive pre- and post-operative cortisone therapy. When the adrenal inadequacy is likely to be severe it is advisable to give cortisone acetate, 100 mg. intramuscularly, twenty-four and twelve hours before operation and every twelve hours postoperatively for the first forty-eight hours after operation, reducing the dose to 50 mg. for the next two days. Subsequent therapy can be by oral administration as required. In the event of collapse occurring during operation in such a patient, 100 to 150 mg. of hydrocortisone should be administered intravenously.

References

Ablett, J. J. L. (1956): *Brit. J. Anæsth.*, **28,** 258.
Boivin, P. A., Hudon, F., and Jacques, A. (1958): *Canad. Anæsth. Soc. J.*, **5,** 409.
Bourne, J. G. (1957): *Lancet*, **ii,** 499.
Brindle, G. F., Gilbert, R. G. B., and Millar, R. A. (1957); *Canad. Anæsth. Soc. J.*, **4,** 265.
Brown, D. (1959): *Anæsthesia*, **14,** 135.
Brown, T. A., and Woods, M. A. (1958): *Brit. J. Anæsth.*, **30,** 338.
Burn, J. H., Epstein, H. G., Feigan, C. A., and Paton, W. D. M. (1957): *Brit. med. J.*, **ii,** 479.
——, and Epstein, H. G. (1959): *Brit. J. Anæsth.*, **31,** 199.
Burton, G. W., and Battersby, T. G. (1958): *Dent. Practit. Rec.*, **4,** 91.
Churchill-Davidson, H. C., and Richardson, A. T. (1957): *Lancet*, **i,** 1223.
Dobkin, A. B. (1958): In 'Modern Trends in Anæsthesia', edited by F. T. Evans and T. C. Gray, London.
——, Drummond, K., and Purkin, N. (1959): *Brit. J. Anæsth.*, **31,** 53.
Drew, C. E., and Anderson, I. M. (1959): *Ibid.*, **i,** 748.
——, Keen, G., and Benazan, D. B. (1959): *Lancet*, **i,** 745.
Dundee, J. W. (1958): *Brit. med. J.*, **i,** 1433.
——, Linde, H. W., and Dripps, R. D. (1957): *Anesthesiology*, **18,** 66.
Freier, S., Neal, B. W., Nisbet, H. I. A., Rees, G. J., and Wilson, F. (1957): *Brit. med. J.*, **i,** 1333.
Goldman, V. (1959): *Curr. Res. Anesth.*, **38,** 192.
Griffin, S. G., Nattrass, F. J., and Pask, E. A. (1956): *Lancet*, **ii,** 704.
Halton, J. (1959): Personal communication and article submitted for publication.
Hudon, F., Jacques, A., and Boivin, P. (1958): *Canad. Anæsth. Soc. J.*, **5,** 403.
Johnstone, M. (1958): *Brit. J. Anæsth.*, **30,** 435.
Klock, J. H. (1955): *Curr. Res. Anesth.*, **34,** 379.
Krantz, J. C., Jr., Carr, J., Lee, G., and Bell, F. K. (1953): *J. Pharmacol. exp. Ther.*, **108,** 488.
Lassen, H. C. A. (1953): *Lancet*, **i,** 37.
Lu, G., Ling, S. G., and Krantz, J. C., Jr. (1953): *Anesthesiology*, **14,** 466.
McGregor, M., Davenport, D., Jegier, W., Sekelj, P., Gibbons, J. E., and Demers, P. P. (1958): *Brit. J. Anæsth.*, **30,** 398.
Macphee, I. W., Gray, T. C., and Davis, Sheila M. (1958): *Lancet*, **ii,** 1196.
Mapleson, W. W. (1957): *Brit. med. J.*, **ii,** 488.
Marrett, H. R. (1957): *Ibid.*, **ii,** 331.
Most van Spijk, D. V. D., and Lammers, W. (1957): *Lancet*, **ii,** 94.
Mushin, W. W., Rendell Baker, L., and Thompson, P. W. (1959): 'Automatic Ventilation of the Lungs', Oxford.
Newman, H. C. (1958); *Brit. J. Anæsth.*, **30,** 555.
Nisbet, H. I. A. (1959): *Brit. med. J.*, **i,** 95.
——, and Wilson, F. (1959): In the press.
Pope, E. S. (1957): *Anæsthesia*, **12,** 405.
Pulver, R. (1955): *Arch. exp. Path. Pharm.*, **228,** 172.
Raventós, J. (1956): *Brit. J. Pharmacol.*, **11,** 394.
——, and Dee, J. (1959): *Brit. J. Anæsth.*, **31,** 46.
Robbins, B. H. (1946): *J. Pharmacol. exp. Ther.*, **86,** 197.
Robson, J. C., and Sheridan, C. S. (1957): *Curr. Res. Anesth.*, **36,** 63.
Severinghouse, J. W., and Cullen, S. C. (1958): *Anesthesiology*, **19,** 165.
Stephen, C. R., Grosskrewtz, D. C., Lawrence, J. H. A., Fabian, L. W., and Bowglois-Gabardin, M. (1957): *Canad. Anæsth. Soc. J.*, **4,** 246.
Tom, A. (1956): *Brit. med. J.*, **i,** 1085.
Walsh, (1958): *Brit. J. Anæsth.*, **30,** 578.
Wyant, G. M., Merrieman, J. E., Kilduff, C. J., and Thomas, E. T. (1958): *Canad. Anesth. Soc. J.*, **5,** 384.
Wylie, W. D. (1956): *The Practitioner*, **177,** 481.

ADVANCES IN RADIOTHERAPY

By T. M. PROSSOR, B.Sc., F.R.C.S.Ed., F.F.R.
Radiotherapist, Westminster Hospital

WHATEVER the future may hold in the way of treatment for malignant tumours, be it surgery or hormones, anti-metabolites, anti-mitotics, irradiation alone, or in combination with one or all of these agents, there is no shadow of doubt that radiotherapy continues to advance with an acceleration which justifies constant revision and reconsideration of our therapeutic methods in an attempt to improve the control of the disease.

Although gamma rays from radium have been used for the treatment of relatively accessible malignant tumours for thirty years, the management of extensive and deeply placed tumours by irradiation depended upon x-rays generated at 250 kV—the so-called conventional x-rays. Where large volumes of tissue had to be treated, it was often difficult or impossible to deliver an adequate tumour dose to the whole volume without grave risk of serious blood changes, as well as severe irradiation sickness. Nevertheless, in many cases, the radiosensitivity of the tumours proved so great that complete and sometimes lasting regression, even in some metastatic growths, could be achieved. When the disease was accessible, for example in the lip, tongue or the buccal mucosa, it could be implanted with radium needles; indeed the results of this method—interstitial irradiation with the hard gamma-rays from radium needles—have never been surpassed; where applicable it remains the treatment of choice.

Because of the high cost of radium and the limited amounts available, radium beam units usually did not contain more than 10 grammes of radium. This necessitated using a small radium skin distance in order to achieve biologically adequate, as well as economic, dose rates. To those fortunate enough to possess a radium beam unit, however, it became obvious that the hard, more penetrating gamma-beam, equivalent to x-rays generated at 2 Mev., had many advantages to the patient. It caused much less damage to the skin than the conventional x-rays generated at 250 kV; in particular it caused less damage to bone and cartilage. These observations led to the realization that, if sufficiently active sources of gamma radiation or its equivalent supervoltage radiation were forthcoming, these advantages could be utilized. This, together with the enormous advances in nuclear physics, and the developments in high-voltage engineering, has led on the one hand to the use of more active sources of gamma radiation and on the other hand to the development of more powerful x-ray machines.

IRRADIATION BY MEGA-VOLTAGE BEAMS (GAMMA-RAYS OR SUPERVOLTAGE X-RAYS)

There are now available for clinical use machines capable of producing x-rays generated at two, four and even eight million volts. Many of the

larger centres in Britain have already installed and are regularly using such apparatus. The 2 Mev. Van de Graaff type generator has been in use in this country now for nearly a decade. It has proved itself a reliable, robust clinical weapon; more recently it has been superseded by linear accelerators producing x-rays at four or more million volts. Today no centre can be considered complete unless it has such units available. In at least two centres in England and in many in the United States machines of even greater energy, such as betatrons of up to 22 Mev., are already in clinical use.

There is still a vast programme of clinical research to be carried out on these multi-million-volt x-ray beams. Some of the machines are capable of delivering an electron beam for direct irradiation of the tumour with high energy electrons. It is too early yet to assess and evaluate the clinical results observed from treatment with these very powerful machines. It is possible that the optimum voltage level for supervoltage x-rays may be in the four to eight million volt range. There are now in production linear accelerators in the 4 Mev. range with accelerating guides of no more than 1 metre in length, which will thus occupy treatment rooms no larger than those required for the larger cobalt units and which will be as simple to use clinically.

The development of the atomic pile has made available a whole galaxy of radioactive isotopes. Certain of these gamma-ray emitting substances have proved very suitable for beam therapy; of the many available, those which have proved best for this purpose are cobalt^{60}, cæsium^{137} and iridium^{192}. They have made practicable the production of gamma-ray emitting beam units of vastly greater output than ever hitherto envisaged.

The most modern units are of sufficiently great activity to allow long-source skin distances so that they have become equivalent to supervoltage x-ray machines in the 3 million volt range. Moreover, because of their relative simplicity their reliability is correspondingly greater and their maintenance far less costly. Radioactive cobalt (Co^{60}), which is produced by irradiating stable cobalt (Co^{59}) in the neutron flux of an atomic pile, is the most important of the gamma-ray emitters. It has a half-life of 5.3 years and decays, emitting in the process clinically insignificant β-rays and two gamma-rays. For clinical purposes the latter may be regarded as monochromatic and of beam energy of 1.25 Mev. Co^{60} can be produced at a high specific activity so that it has been possible to build telecobalt machines containing 2000 curies or more of the isotope, an amount equivalent to 3000 g. of radium (an unheard-of amount, of course), giving a beam equivalent to that from a 3 million volt x-ray machine. A considerable range of Co^{60} beam units has been built which are admirably suited both for typical multiple beam therapy and for rotating beam therapy. These are compact, and absolutely safe, as regards protection of patient and operators, as well as freely mobile and easily manœuvrable to facilitate ease and accuracy of beam direction to the patient.

CÆSIUM BEAM UNITS

The fission product cæsium^{137} is present in the spent uranium of atomic piles, and production and separation of it in suitable form for concentration for beam units has now been achieved, and such apparatus for clinical application has already been installed in some centres. Cs^{137} has a long half-life—33 years—and the relatively high energy of its monochromatic gamma radiation (equivalent to 1,250 kV x-rays) makes it a valuable replacement for the old outmoded conventional x-rays.

Radio-iridium beam units are of much less importance for teletherapy than those containing either cobalt or cæsium, for it is desirable that gamma sources for this purpose should have a half-life of several years as well as gamma energy higher than say 500 kV to avoid differential absorption in bone and therefore damage to it: radio-iridium possesses neither. It is produced by neutron irradiation of the metal I^{191} and has a half-life of only 75 days, decaying with the emission of β-rays and several gamma-rays of energy between 0.19 and 0.65 Mev., that is equivalent to about 400 kV x-rays. The rapid decay is a major disadvantage and, although it is feasible to renew the source at frequent intervals, it is unlikely that this isotope will come into general use.

ADVANTAGES OF SUPERVOLTAGE IRRADIATION

The advantages of using mega-voltage beams in the 2 to 5 Mev. range are so great that it is not surprising that their wider application and distribution are increasing rapidly. The advantages of the harder radiation are not only due to the increased penetration and the higher percentage depth doses, but are in part also attributable to the lower whole body (integral) dose and in part to the fact that the maximum dose is displaced from the skin surface to a short distance below the skin which is therefore likely to receive far less damage. In addition, the localization of high dose volumes about the tumour area is much sharper than those obtained when the old conventional (200 to 250 kV) beams were used; most important of all, the incidence of differential energy absorption between tissue and bone reduces the considerable risk of bone necrosis at high dose levels. The machines are robust, economical, flexible and for the most part easy to maintain. Generally speaking they allow of easy and accurate application and beam direction. Not satisfied with the many advantages attributable to the mega-voltage beams, radiotherapists and their colleagues, the hospital physicists, have spent much time and effort in attempting to improve the depth dose distributions of the irradiated areas in their patients.

In treating lesions which are deeply situated it is possible to achieve a very high depth dose at the lesion by using a large number of small beams carefully directed to overlap in the depth. A logical extension of this principle is to rotate either the patient, or preferably the apparatus, during treatment so that the tumour volume is continuously irradiated, while the

skin and normal tissues through which the beam must pass to reach it are constantly changing and consequently spared. Moving beam therapy is undoubtedly the simplest and most efficient method at our disposal for increasing the tumour dose at a depth. It is a technical advance of the first magnitude, allowing the use of mega-voltage beams to even greater advantage than inherent in their physical characteristics. It is so useful and allows of such great accuracy that it is rightly becoming more and more generally available.

CLINICAL RESULTS

Progress in the management of malignant disease in the abdomen by radiotherapy using mega-voltage x-ray beams is well illustrated by the observed results of treatment in malignant disease of the testes, carcinoma of the bladder and of the uterus and cervix.

Seminoma.—Hitherto the old conventional x-rays generated at 250 kV were capable of destroying the para-aortic metastases from the relatively radiosensitive seminoma of the testis, but irradiation with this quality cannot deal adequately with the relatively insensitive teratomas, a fact well shown by the survival figures for the two diseases. No less than 75 per cent. of cases of seminoma presenting with no initial clinical evidence of metastases survived five years, following simple orchidectomy and postoperative irradiation. This compares with a figure of 46 per cent. for a similar group of teratomas similarly treated.

Teratoma.—In an attempt to improve the control of this disease by supervoltage irradiation, all cases of teratoma of the testis seen at Westminster Hospital since 1954 have been treated postoperatively by x-rays generated at 2 Mev. No untoward systemic reaction has been observed, and skin reactions have been very mild—slight pigmentation and dry peeling at the worst and only mild erythema in the majority of cases. In no case has any severe desquamation been noted, nor has there been any intestinal injury or kidney damage. Although it is only five years since the first patient in this series completed treatment, it is fair to say that the results are at least encouraging. Of the 42 patients who presented in the first instance without clinical evidence of metastases, 30 are alive and well with no evidence of disease (Prossor, 1959).

Carcinoma of the bladder.—In carcinoma of the bladder radiotherapy by beams in the two to three million volt range has produced results which surpass by far any hitherto observed.

In the Westminster series 58 cases were treated before 1955 and are therefore available for analysis. Twenty-six patients were treated more than five years ago and of these seven are alive and well, representing a five-year survival of 27 per cent., whilst 24 were alive three years after treatment, representing a 41 per cent. three-year survival.

The stage of the disease has an important bearing upon the prognosis. When the growth is of the infiltrating variety, as might be expected the prognosis is much worse.

In eight cases in which the tumour was not infiltrating the bladder wall, five

were alive and well three years after treatment, that is 62.5 per cent. In 50 cases the disease was of the infiltrating variety, and of these only 19 survived three years, that is 38 per cent. Blomfield (1956) reported very similar figures.

Carcinoma of the uterus and cervix.—Patients with carcinoma of the uterus and cervix can now be treated as outpatients, using the rotating beam from the 2000 curie Co^{60} Theratron. Although it is too soon to give a five-year figure, our preliminary results show that the regression of the disease produced, even in advanced cases, compares very favourably with those of the intracavitary irradiation. Patients have tolerated radical treatment better and it is possible to give palliative treatment with far less disturbance to the patient than with conventional x-rays or even intracavitary irradiation with radium.

The decrease in the amount of lateral scatter and the improvement in the sharpness of collimation of the supervoltage beams allow of minimal dosage to structures outside it and the total body dose and integral dose is far less than that for similar field size with conventional x-rays. Finally the abdomen and pelvis tolerate well doses of the order of 6000r in six weeks. In fact, in the words of Sir Stanford Cade, these supervoltage beams are considerate to the patient, very gentle in their action on bone and normal tissues surrounding the tumours, while remaining capable of producing very satisfactory and lasting regression of the disease, even in the abdominal metastases from such resistant tumours as teratomas of the testis.

COMBINED THERAPY

It is not the purpose here to discuss in detail the whole vast field of progress in the relationship of surgery, irradiation and chemotherapy in the management of hormone-dependent and independent cancers, but, in considering the forward advance in radiotherapy, it is of the utmost importance to bear in mind that it is bound inseparably to the other two. Chemotherapy is still in its early stages but of increasing importance. Progress in either or both may well depend as much on the success with which cooperation and collaboration between them is achieved as upon the construction of new and more powerful machines or the introduction of new compounds.

This philosophy is well illustrated by the modern attitudes towards the management of cancer of the breast. It has long ago been shown that the treatment of choice in early cases is radical mastectomy, and that where there are axillary metastatic glands, or where the tumour is fixed to the skin or deeply, radiotherapy alone or with hormones is the treatment to be preferred. Even when there are isolated bony metastases irradiation can often produce dramatic relief of pain, and re-calcification; when the disease is disseminated, bilateral adrenalectomy and oöphorectomy or hypophysectomy can often induce profound and prolonged remission of the disease.

The total surgical removal of the pituitary is technically difficult to achieve. Ablation by piecemeal surgical removal invariably leaves remnants of the gland behind and to complete its destruction radon seeds or radio-

active yttrium are introduced into the sella turcica at the completion of the operation. Many ingenious methods for destroying the gland by irradiation alone have been attempted. Radon seeds or radioactive yttrium have been introduced into the sella turcica by way of the nose and sphenoidal sinus (Forrest *et al.*, 1956), but the danger of damage to the chiasma and consequent blindness, meningitis, and cerebral spinal rhinorrhœa has led to this method being abandoned in many centres. More recently a method for introducing a radioactive source of yttrium but avoiding these hazardous complications has been devised. In this new method a cylindrical rod of yttrium is encased in a thin, sharply pointed nylon sheath which is fitted into one end of a stainless steel self-tapping screw. Under radiological control with an image intensifier, this is inserted, via the nose, through the anterior wall of the sella turcica which is thus plugged, so preventing the troublesome complication of rhinorrhœa. At the same time the sources of irradiation are placed with constant accuracy, and held in the optimum position, thus avoiding damage to the chiasma and ensuring complete destruction by irradiation of the gland. The pituitary can also be irradiated by beams from the 4 Mev. linear accelerator and by beams of protons from the cyclotron (Lawrence and Tobias, 1956; Tobias *et al.*, 1958).

Pari passu with the progress of surgery and irradiation in the management of hormone-dependent cancers is the introduction of chemical methods of increasing the radio-sensitivity of certain tumours. It has been shown (Gray *et al.*, 1953) that supersaturation of certain malignant tumours with oxygen renders them more vulnerable to irradiation. Of particular importance is the clinical observation by Farber (1958) of the potentiation by the anti-metabolite actinomycin D of the radiotherapeutic effect, especially on the notoriously radio-resistant rhabdomyosarcoma.

Among the most recent forward advances in radiotherapy is the new technique of transfusion of autogenous bone marrow following heavy doses of irradiation by mega-voltage beams to the whole thorax in the treatment of pulmonary metastases (Newton *et al.*, 1959). Worth-while regression of widespread disease has been achieved while hæmatological depression from extensive irradiation of bone marrow has been avoided by the transfusion.

It is researches such as these which are continuing to make modern radiotherapy a more powerful weapon against cancer.

References

Blomfield, G. W. (1956): *J. Fac. Radiol. (Lond.)*, **7**, 260.
Farber, Sidney (1958): Seventh International Cancer Congress, Abstract of Papers.
Forrest, A. P. M. *et al.* (1956): *Lancet*, **i**, 399.
Gray, L. H., *et al.* (1953): *Brit. J. Radiol.*, **26**, 638.
Lawrence, J. H., and Tobias, C. A. (1956): *Cancer Res.*, **16**, 185.
Newton, K. A., *et al.* (1959): *Brit. med. J.*, **i**, 531.
Prossor, T. M. (1959): *Proc. Roy. Soc. Med.*, **52**, 340.
Tobias, C. A., *et al.* (1958): *Cancer Res.*, **18**, 121.

ADVANCES IN REHABILITATION

By HOWARD A. RUSK, M.D.

Department of Physical Medicine and Rehabilitation, New York University College of Medicine, New York City

THE greatest advance that has been made in the rehabilitation of the physically handicapped is the new acceptance of a third dimension of medical responsibility.

THE 'THIRD PHASE OF MEDICINE'

Rehabilitation has often been termed the 'third phase of medicine', following 'preventive medicine' and 'curative medicine and surgery'. It is that period when the 'fever is down and the stitches are out', the period 'between the bed and the job'. In contrast to 'convalescence', in which the patient is left alone to let nature and time take their course, rehabilitation is a dynamic concept in which the skills of the rehabilitation team, consisting of the physician, physical therapists, occupational therapists, nurses, social workers, counsellors and other trained personnel, are integrated as a single force to assist the patient in reaching the maximum of his physical, emotional and social and vocational potentials.

The first objective of rehabilitation is to eliminate the physical disability if that is possible; the second, to reduce or alleviate the disability to the greatest extent possible; and the third, to retrain the person with a residual physical disability 'to live and to work within the limits of his disability but to the hilt of his capabilities'.

PRESENT-DAY PROBLEMS

Until the last fifty years, the saving of human life as the traditional and cherished goal of medicine was largely a matter of saving individual patients. With the first half of the twentieth century, the whole character of medicine's traditional goal was changed. The expansion of research into the etiology and therapy of communicable and infectious diseases 'struck specifics'. The establishment of new and effective public health measures and the rich findings in the basic fields reported elsewhere in this Special Number of *The Practitioner* gave the life-saving functions of medicine mass proportions. These, combined with similar advances in greater availability of medical and hospital care, improved nutrition, increased education, better housing and all the contributing factors to our unprecedented current standard of living, mean that hundreds of thousands of persons are alive today who at the turn of the century would have died with the same medical problems. Yet many of them have not come out unscathed. They have survived only to find themselves confronted with residual disability. The paraplegic whose back is broken in a fall does not die today as he would

have done fifty years ago. He has strong arms, an active mind and a burning desire to live the best life he can with what he has left. Antibiotics control the upper respiratory and urinary infections of the severely involved cerebral palsied youngster who would have succumbed before their development. He seeks his place in society. The survivors of infection get their share of the degenerative diseases. These are present-day problems which must be solved.

The day-to-day experience of all practising physicians shows that not only has there been a substantial increase in the gross number of disabled persons, but that a growing percentage of our population suffer from long-term illnesses and substantial physical impairments. Two thousand years ago the average length of life was but twenty-five years; at the turn of the century, it was forty-nine; by 1950 it had reached sixty-seven; and we are now on the threshold of the legendary three-score and ten. Contrary to opinions expressed by some, the growing incidence of chronic disability is a tribute to medicine rather than an indictment. But as the physician has been largely responsible for this development, he must assume leadership in its solution.

EXPANDING OPPORTUNITIES

One of the most significant medical and social advances of the past decade is the growing interest, both professional and among the public, throughout the world of the development of rehabilitation services for the physically handicapped. Undoubtedly, much of this interest in expanding rehabilitation opportunities and services for the handicapped has resulted both directly and indirectly from the 1939-45 War, when attention was focused on the problems of disabled servicemen. Such advances, however, are not entirely due to this impetus, as the growth of rehabilitation services for the handicapped is a part of a total pattern of an expanding community, national and global consciousness of social welfare, which is reflected in similar advances in all educational, health, and social services. As in all great social movements, this increased interest in rehabilitation has been a result of the impact and recognition of increased needs: in this instance, the rapid increase in the developed parts of the world of the incidence of chronic disability as a result of the increasing age of the population.

Although some nations of the world still have pressing problems of communicable disease, and life expectancy rates vary from nation to nation, depending upon the availability of medical care, public health measures, food supply, and the general standard of living, the trend in all nations is towards a greatly increased life expectancy, with the result that throughout the world the population is gradually becoming older. At the same time that the average age is advancing in the developed parts of the world, a new concept of the dignity of man and the value of the worth of the individual is beginning to emerge in those nations of the world which do not have the benefits as yet of modern programmes of public health and medical care.

This new concept of the worth of the individual has been symbolized, and is finding its expression in many instances in the desire of these nations to institute programmes of services for their physically handicapped.

Rehabilitation has been defined as the ultimate restoration of the disabled person to his maximum capacity—physical, emotional, social and vocational. Implicit in this definition is the need for a team whose members can bring together a wide variety of skills and understandings. No one profession can furnish all the services needed. Rather is rehabilitation an area of specialized activity within a number of professional disciplines.

THE PHYSICIAN'S RESPONSIBILITY

Until recent years, the great majority of the medical profession looked upon rehabilitation as an extra-curricular activity of medicine: something dealing with social work and vocational training, but something which had little concern, and which held but few implications, for medicine. Today, however, that trend is being reversed and, although there are still many physicians who are unfamiliar with the aims and procedures of rehabilitation, more and more is medicine beginning to recognize that medical care cannot be considered complete until the patient with a residual physical disability has been trained 'to live and work with what he has left'. Except in a few isolated instances, the physically handicapped person must be retrained to walk and travel, to care for his daily needs, to use normal methods of transportation, to use ordinary toilet facilities, to apply and remove his own prosthetic devices and to communicate either orally or in writing. These are such simple things that they are often overlooked, but the personal, vocational, and social success of the handicapped person is dependent upon them.

The practice of rehabilitation for the general practitioner, or for any doctor, begins with the belief in the basic philosophy that the doctor's responsibility does not end when the acute illness is ended or surgery is completed; it ends only when the individual is retrained to live and work with what is left. This basic concept of the doctor's responsibility can be achieved only if rehabilitation is considered an integral part of medical services. Any programme of rehabilitation is only as sound as the basic medical service of which it is a part. The diagnosis and prognosis must be accurate, for it is upon them that the feasibility of retraining is determined.

REHABILITATION SERVICES IN HOSPITALS

Although some outstanding rehabilitation programmes in various parts of the world have demonstrated that rehabilitation to the point of self-care and even to full or limited employment is possible for many of the chronically ill who have been hospitalized for long periods, patients in few hospitals receive comprehensive rehabilitation service. Hospitals complain that the chronically ill are responsible for their overcrowding, but few of them provide the third phase of medical care which will permit many of these patients to leave the hospital.

Just as certain specialized centres for the care of particular diseases requiring specialized personnel and facilities have developed, there has been a trend in the United States, particularly since the last war, to develop 'rehabilitation centres'. In some instances, these 'centres' have been distinct

FIG. 1.—The Institute of Physical Medicine and Rehabilitation, New York University-Bellevue Medical Center.

public or non-profit institutions designed to serve all physicians and all hospitals, but have had no direct affiliations with hospitals. Others have been integral parts of hospitals or medical centres. As compared with but a small handful of such facilities before the 1939-45 War, the total now numbers well over a hundred. Although these independent 'rehabilitation centres' provide a valuable and needed service within a community, if any major attack is to be made on the problems of disability there must be an expansion of rehabilitation services in general hospitals, for it is to the general hospitals that the practising physicians turn for the care of their patients. It is also within the general hospital that such services can be brought to the patient at the earliest possible time, and costly and damaging physical, emotional, social and vocational sequelæ of the acute disease process or trauma be alleviated or minimized. To ignore the development of rehabilitation services within general hospitals is to guarantee the continued deterioration of many less severely disabled persons until they, too, reach the severely disabled and totally dependent category. The neglect of disability is far more costly than an early aggressive programme of rehabilitation which restores the individual to the highest possible level of physical, economic, social and emotional self-sufficiency.

Twelve years of experience in the first comprehensive rehabilitation service in a general civilian hospital—Bellevue Hospital, New York City (fig. 1)—together with extended observation and study of other general hospitals, indicate that rehabilitation services within the hospital can best be provided by the organization of a 'bed service' which has a relationship

to the other hospital services similar to that of the x-ray and laboratory divisions. For example, in Bellevue Hospital the rehabilitation service provides consultants for each of the other major services such as fractures, pædiatrics, surgery, and neurology. Its resident and visiting staff regularly makes rounds with the resident and visiting staff of these services. Its staff may, for example, see a patient in consultation before his leg is removed, indoctrinating him as to what he must expect, why he cannot keep his stump on a pillow, why he has to lie on his abdomen. Medical responsibility during the period of definitive care, of course, rests with the initial or admitting service. As soon as the stitches are removed, the patient is transferred to a rehabilitation ward. At this time, the rehabilitation service assumes the major responsibility for his care, fitting of the prosthesis, and training in its uses. The roles are now reversed; the surgical service has become the consulting service.

Before the actual transfer of the patient to a rehabilitation ward, however, he attends one of the rehabilitation service's semi-weekly evaluation clinics, where his problem is analysed and discussed by all members of the staff—physical therapists, occupational therapists, nurses, vocational counsellors,

FIG. 2.—A view of Goldwater Memorial Hospital on Welfare Island in New York City. One of these buildings houses the Homestead Project.

speech therapists, social workers and psychologists—as well as resident and visiting medical staff. The decision as to the feasibility of transferring the patient to the rehabilitation service is then made on the basis of the service's ability to contribute to his over-all physical, emotional, social and vocational rehabilitation.

PLANNING FOR THE CHRONICALLY DISABLED

One of the major problems now confronting medicine, which will be further accentuated in the next twenty years by the growing incidence of chronic disease and chronic disability, is how these services can be brought most effectively and most economically to those patients needing them.

Physicians, hospitals, social workers, community agencies and families err

constantly in the loose interpretation of the term 'chronic illness'. A recent government publication in the United States reports that: 'in 1950, 17 in every 100 persons aged 65 and over were estimated to have a long-term disabling chronic illness, as compared to 3 or 4 per cent. per 100 among the

FIG. 3.—A patient's room in the Homestead Project.

general population'. Among these 17 in every 100 persons aged 65 and over, there are many who are 'chronically ill' in that they require continuing medical services of the type which can be provided only or best within a hospital. Among them, however, are others who are 'chronically disabled' in that although they have static physical impairments (such as hemiplegia following a stroke), they are not in need of continuing hospital care. But since there is nowhere else for them to go, they are forced to live for months or years in an environment where pain and death are a part of the daily routine.

This situation was brought into the professional spotlight recently by a study conducted under the auspices of the New York Foundation at Goldwater Memorial Hospital, a municipal hospital of the City of New York. In this study of 95 unselected cases (average age, 68.5 years), it was found after intensive medical, social, psychological and economic evaluation, that only seven were felt to be in need of continuing hospitalization; and there was considerable doubt about this in two of them. Using the customary rehabilitation standards, 11 patients were considered suitable for rehabilitation with a better than 50 : 50 prospect of success. The remaining 84 of the original 95 patients were considered to be in no need of either rehabilitation or definitive medical care. An analysis of but three of these patients showed they alone had been cared for in municipal facilities for a total of nearly 19,000 days. Calculating arbitrarily and conservatively at $12 per day as cost for their care, the total cost of these three patients alone to that point was $228,000 and the end was not in sight. This is a sizeable sum, but it is only money. What about the cost to these three individuals in boredom, anxiety, frustration and resignation?

'HOMESTEADS'

Following this initial study, a subsequent study was made in which it was found that one out of every five patients in New York City's huge municipal hospital system was there not because he needed hospital services, but simply because he had no place to go. Currently the City of New York is engaged in remedying this situation by the creation of a new type of institution known as a 'homestead' (fig. 2, 3, 4). These new institutions created through the modification of existing, unneeded buildings, are adjacent to municipal hospitals so that the residents of the 'homesteads' may be immediately transferred into hospitals should they need medical care from time to time.

With this new approach, New York City will save substantial sums and at the same time the residents of the new 'homesteads' will have much richer and fuller lives than in hospitals where they are surrounded by illness and must conform to hospital régimes which are unrelated to their needs.

PLANNING FOR THE AGED

Like other national and community problems, the very size and complexity of development of services for our aged makes over-all planning for such services difficult. Even though we have failed at both the national and community levels to make adequate preparations to meet the complex and

FIG. 4.—The patients' library which serves all patients at the Goldwater Memorial Hospital which includes the Homestead Project.

multiple needs of our increasing number of aged, this does not prevent action programmes designed to solve or alleviate at least one aspect of the problem. This is what New York City is doing with its 'homesteads'. These will not solve the problems of the city's aged, but they will at least alleviate one aspect of the problem.

Although it is generally agreed that there are no diseases exclusively

characteristic of ageing, experience strongly supports the statistical findings that elderly people take a disproportionate share in the chronic and disabling diseases. This does not necessarily indicate a need for separation of medical and health services for the aged from those for the young, but rather an adaptation and extension of existing resources to suit their special needs. The ageing patients constitute perhaps the largest single group which could benefit from an extension of home-care services to provide them with the necessary medical and nursing help after their discharge from the hospital. The addition of medical rehabilitation to the conventional clinical services has enabled many an elderly man and woman, previously considered hopelessly crippled, to regain his or her functional independence and continue to live without burden to themselves or their environment. While clinical medicine continually strives to free the elderly from the distressing physical and mental illnesses, the basic biological sciences endeavour to explain the many enigmatic questions connected with ageing.

CONCLUSION

Rehabilitation during the first quarter of the century was characterized by the development of orthopædic surgery, physical therapy, occupational therapy, and the State-Federal vocational rehabilitation programmes, all outgrowths of the 1914-18 War. Under the stimulus of the 1939-45 War, the second quarter of the century has seen a recognition that the problems medicine faces in meeting the growing incidence of chronic disease and disability extend far beyond any medical specialty; they are problems which must be faced and solved by medicine as a whole. The concept of rehabilitation and the basic techniques must be made a part of the armamentarium of all physicians, for regardless of the type of disability the responsibility of the physician to his patient cannot end when the acute injury or illness has been cared for. Medical care is not complete until the patient has been trained to live and to work with what he has left.

If any major attack is to be made on the problems of chronic disability, the general hospital and the individual practising physician must be the focal points of that attack. It is only in doctors' surgeries and in general hospitals that such services can be brought to the patient at the earliest possible time and that the costly and damaging physical, emotional, social and vocational sequelæ of the acute disease process or trauma may be alleviated or minimized.

Rehabilitation of the chronically ill and the chronically disabled is not just a series of restorative techniques: it is a philosophy of medical responsibility. Failure to assume this responsibility means to guarantee the continued deterioration of many less severely disabled persons until they, too, reach the severely disabled and totally dependent category. The neglect of disability in its early stages is far more costly than an early aggressive programme of rehabilitation which restores the individual to the highest possible level of physical, economic, social and emotional self-sufficiency.

ADVANCES IN GENERAL PRACTICE

By D. G. FRENCH, M.D.

Kidsgrove, Staffordshire

THERE are few developments in medicine which do not affect the conduct of general practice in some way, and the advances in the past two decades have been so rapid that the general practitioner is hard pressed to keep abreast of all that is new. He will never have to do a mitral valvotomy or repair an atrial septal defect but he must know that these operations can be done, where they are done and what are the indications for, and prognosis of, these operations and others like them. It follows that many conditions, the exact diagnosis of which used to be little more than an academic exercise, must now be much more thoroughly understood and this is especially applicable to the rapidly expanding spheres of thoracic and cardiac surgery. When new discoveries and advances are made, the applications are at first confined to one or two hospitals and only gradually become generally accepted practice. This time-lag is very variable and may depend upon the supply of adequate quantities of a new drug, for example, streptomycin, or upon the training of the requisite teams in new and difficult techniques, as in cardiac surgery, in which not only have surgeons, anæsthetists and theatre teams needed long preparation, but also the work of cardiologists has required complete reorientation. The last article on advances in general practice appeared two years ago and much that was new then is only now being adopted on a scale large enough to concern all general practitioners. The past two years have been a period of consolidation during which there have been no bombshells comparable to the introduction of 'prontosil'.

HYPERTENSION

The most important advances have concerned the management of hypertension and cardiovascular diseases. The newer oral diuretics are potent and are proving to be very versatile. They have been shown to be most useful in the management of congestive heart failure, hypertension and toxæmia of pregnancy and have a place in the treatment of some forms of migraine, nephritis, premenstrual œdema and ascites. Their use requires some care, especially in hypertension, in which they potentiate the action of ganglion-blocking agents, the dosage of which may have to be reduced.

Of the many ganglion-blocking agents used in the management of hypertension, one might single out mecamylamine hydrochloride, which has been found to be most suitable for use in general practice, especially when used with hydrochlorothiazide. This combination forms a useful basis to which other hypotensive agents may be added, such as pempidine or phenoxybenzamine, when the hypertension is difficult to control.

The whole approach to hypertension, however, requires more thought than it commonly receives. Much of the current confusion of thought is attributable to the sales propaganda of the drug houses. One wonders how many patients with mild hypertension are given prolonged and inadequate treatment with these potent and expensive new hypotensive drugs when in reality all that is required is weight reduction, mild sedation and reassurance. Even when the hypertension is sufficiently severe to warrant active hypotensive treatment, do we always ask ourselves if we are prepared to supervise the treatment efficiently before embarking on it? In general, it is unwise to press the treatment to the point of achieving 'normal' blood pressure levels, as this incurs considerable risk of cerebral vascular thrombosis, and iatrogenic hemiplegia can be a tragic reminder of our misguided enthusiasm. Patients should be warned that quite moderate amounts of alcohol can produce a vasodilatation which is sufficient to lower to dangerous levels the blood pressure already reduced by these drugs: I have one patient whose cerebral thrombosis occurred while he was driving home from a party. It is most important to keep clearly before us the realization that, though these recent advances are helping us to control blood pressure to some extent, they have little or no effect on an already diseased vascular tree and that this pathological process is not uniformly distributed; a soft radial artery is no guarantee that cerebral or coronary vessels are not atheromatous and prone to intravascular clotting.

VASCULAR DISEASE

Diabetes mellitus is one of the commonest causes of vascular disease, and its management is gradually being taken out of the hands of general practitioners by the establishment of diabetic clinics in the large hospitals. If this does in truth show improved results, it is a reflection on the quality of general practice because there is no reason why these cases should not be satisfactorily managed at home with only occasional assistance from specialists and laboratories (Pinsent, 1958). Although it is a trend which is to be deplored, it must be conceded that, as the National Health Service is based on a per capita system of payment and as patients make progressively greater demands on our time in their search for physical and mental perfection, it is sometimes a relief to be able to spread the load.

The after-care of patients who have had thrombotic or embolic incidents is gradually altering. Opinion is still divided on the value of prolonged anticoagulant therapy after coronary thrombosis, the extreme view being taken by Evans (1959) who calls this 'therapeusis through wishful thinking' and condemns it as a useless waste of time. Supporters of anticoagulant therapy looked forward to the recent report of the Medical Research Council (1959) in the hope that it would produce irrefutable proof of its efficacy, but it did not quite do this and is unlikely to bring about any profound change in policy. It is therefore probable that whether one's patients receive this after-treatment or not will continue to depend upon

the views held by the cardiologist of one's choice; and even then, there is almost certain to be some degree of selection as many pathological departments are already unable to deal with the large and growing demands for prothrombin estimations.

Anticoagulants have a more assured place in the short-term prophylaxis and treatment of embolism, especially in heart surgery and major abdominal and pelvic surgery when followed by venous thrombosis, though this is no immediate concern of the general practitioner.

Angiography and surgical embolectomy are two techniques which are being practised on a greater scale. Peripheral vascular embolism most commonly occurs in association with atrial fibrillation (Jacobs, 1959) and early diagnosis is essential for embolectomy to be of any use. Within the last few years, angiography has shown that carotid artery occlusion is commoner than was previously thought and is responsible for some unusual syndromes.

DISEASES OF THE HEART

Advances in cardiac surgery continue to emphasize the need for better diagnosis of heart conditions in general practice. Only a few years ago it was almost enough to know that a murmur existed and greater precision was academic; if failure occurred, rest in bed and the administration of digitalis were the essentials of treatment. Today, the surgical treatment of mitral stenosis, patent ductus arteriosus and Fallot's tetralogy is commonplace, and more centres are becoming capable of dealing with septal defects, aortic valve disease and coarctation of the aorta, with the result that the bedside diagnosis of these conditions assumes ever-increasing importance. Leatham (1958) has made a most valuable contribution to the understanding of auscultation of the heart and no-one, whether general practitioner or consultant, should fail to read and digest his Goulstonian Lectures.

The treatment of heart failure continues to improve. Hypertensive heart failure usually responds in the first place to rest in bed and treatment of the hypertension on the lines already mentioned and the newer oral diuretics have an important place in the treatment of most forms of heart failure; in intractable heart failure, their effect may be enhanced by combination with steroids (Mickerson and Swale, 1959). Carbimazole is now used more often than thiouracil in the treatment of thyrotoxic heart disease and is occasionally used in other forms of heart failure, presumably to reduce the metabolic rate and the load on the heart.

The prophylaxis of rheumatic heart disease has become a reality in recent years by the general adoption of prolonged after-treatment of rheumatic fever with penicillin in doses of the order of 250,000 units orally once a day continued for five years; attacks of tonsillitis in these patients should be treated energetically with penicillin by injection, and they should never be allowed to have dental extractions without adequate penicillin treatment before and after.

CORTICOSTEROIDS

The use of corticosteroids in general practice is a controversial subject. These powerful drugs are still something of a novelty and are often misused. They may be valuable in the treatment of rheumatoid arthritis but not all cases do well on them and in general practice the selection of cases must be made by trial and error. If they are not prescribed, the patient is not slow to produce a tablet given by a friend and the request for a supply is difficult to refuse. It is wise to prescribe small quantities so that the patient can be seen for review at frequent intervals. Some asthmatic children seem to do well on them but one would like to see their use confined to status asthmaticus, in which they can be life-saving. They have a wide range of genuine usefulness in topical preparations for the skin and as eye-drops; here the general practitioner is on safer ground and is less likely to do much harm. There is a tendency to give them a trial for all sorts of ill-defined aches and pains but in view of their cost and dangerous side-effects, this should be avoided. Apart from their topical use, little would have been lost if they had been kept under hospital control.

HÆMATOLOGY

There is probably more research being done in hæmatology than in any other branch of medicine and some of it will have far-reaching effects. It is interesting to note that the recently evolved treatment of mammary carcinoma (Watson and Turner, 1959) is a direct descendant of Wilkinson's original work on the treatment of leukæmia (1955). It is necessary, however, to keep the perspective right and to remember that anæmia in general practice is almost synonymous with iron-deficiency anæmia (French, 1955). Addisonian pernicious anæmia may be diagnosed about once a year in an average practice of 2,500 patients and all other forms of anæmia are statistically insignificant with the exception of megaloblastic anæmia of pregnancy which is now being diagnosed with increasing frequency. In a recent survey in this practice (French, 1958), in which 500 patients of both sexes over the age of 50 were examined, more than 10 per cent. were found to have hæmoglobin levels of less than 80 per cent. (11.6 g. per cent.). In view of the numerical importance of iron-deficiency anæmia, it is fair to state that there have been no important advances in hæmatology applicable to general practice since the introduction of parenteral iron therapy.

TUBERCULOSIS

Recent advances in the diagnosis and treatment of pulmonary tuberculosis outside general practice have rendered this a rare consulting-room diagnosis and we are in danger of missing cases through omitting it from our differential diagnosis, but this is to a large extent academic as our patients are subjected to mass radiography at such frequent intervals that no case should escape detection for long. The point is important, however, as tuberculosis of glands, bones and joints in the elderly is liable to be over-

looked. Pulmonary tuberculosis in young adults is still a serious disease and the success of modern chemotherapy should not blind us to the necessity of treatment in sanatoria, as strict discipline is difficult to maintain in the home.

GERIATRICS

The introduction of antibiotics augmented the problem of managing old people with incurable disease, and the growth of geriatrics into a separate specialty with its own organization and administration is one of the changes most appreciated by general practitioners. It is unnecessary to enlarge on the magnitude of this problem of the ageing population nor is it intended to pretend that it has now been solved. But it is pleasant to know that the situation is in hand and that this hitherto unrelieved black spot is now a shade of grey. Many of the beds put at the disposal of the elderly sick are the direct result of the success of the treatment of pulmonary tuberculosis and the whole scheme is gradually taking shape with a minimum of new building. The provision of domestic help is an innovation which is most appreciated and which is often sufficient to enable an old person who would otherwise need institutional care to continue to live at home.

MIDWIFERY

The recommendations of the Cranbrook Committee are intended to improve the standards of domiciliary midwifery, although there are numerous practices doing work of a high standard in which many of the recommended changes would pass unnoticed. For many years the practice of midwifery has been undergoing continuous change and improvement and today there can be few doctors who provide only that minimum attention required by the Maternity Services of the National Health Service. It is now common practice to have special sessions for ante- and post-natal examinations; a quieter atmosphere prevails and the routine is more easily maintained than when these cases are taken in their turn from the general assortment of an ordinary waiting-room population. The diploma in obstetrics of the Royal College of Obstetricians and Gynæcologists is firmly established and is a valuable contribution to the practice of better midwifery.

The prevailing custom of prescribing oral iron preparations throughout the whole of pregnancy requires thought as it appears to be a very casual approach to the problem. If iron deficiency exists it should be diagnosed during efficient antenatal care and treated accordingly; if it does not exist, there is no need for iron. After the 26th week, oral iron therapy is not very effective and parenteral iron therapy should then be used when iron-deficiency anæmia has been diagnosed.

STANDARDS IN GENERAL PRACTICE

There are other important trends which should contribute to a sustained improvement in the standards of general practice. Practice vacancies are now filled by selection; in other words, a competitive element has been

introduced and young doctors may have long and frustrating waits before becoming established. Those who have the foresight to see the inevitability of this period of probation and who spend the time doing a thoughtfully planned series of carefully selected hospital appointments, acquire experience which cannot be ignored by selection committees. Some of the applicants are men who have reached senior registrar level and hold higher qualifications. Thus, the young entrants into general practice are incomparably better trained and more experienced than their pre-war counterparts who could, if they chose, enter general practice immediately after graduating, and one would expect this change to improve the standards and quality of work in general practice.

The College of General Practitioners is actively concerned with the maintenance of high standards in general practice and has already done much to stimulate interest in postgraduate study. Most refresher courses are arranged in collaboration with the College and the recently introduced Recording Service is a most interesting and valuable innovation, the object of which was to bring postgraduate instruction to practitioners who found it difficult to attend teaching centres. Talks are recorded on magnetic tape and long-playing gramophone records and are sent to members of the College who have asked to receive them.

The present widespread interest in research in general practice was mainly initiated or stimulated by the College and has been encouraged by the awards of grants and scholarships by the British Medical Association and several of the large drug houses. Anything which promotes continued interest in the work of general practice is a good thing and the subject of merit awards should be considered in this light.

CONCLUSION

Most of the general practitioner's time is taken up with things which occur commonly and for that reason this thumb-nail sketch of advances and trends has been confined to the larger problems. Research in cancer, hæmatology and virology appears to be on the brink of producing results of fundamental importance and we look to the not-distant future with unbounded optimism.

References

Evans, W. (1959): *Brit. med. J.*, **i**, 249.
French, D. G. (1955): *Proc. Roy. Soc. Med.*, **48**, 347.
—— (1958): 'British Encyclopædia of Medical Practice'. 'Interim Supplement' 190, London, p. 2.
Jacobs, A. L. (1959): *Proc. Roy. Soc. Med.*, **52**, 159.
Leatham, A. (1958): *Lancet*, **i**, 703, 757.
Medical Research Council (1959): *Brit. med. J.*, **i**, 803.
Mickerson, J. N., and Swale, J. (1959): *Ibid.*, **i**, 876.
Pinsent, R. J. F. H. (1958): Recording Service (Diabetes), College of General Practitioners.
Watson, G. W., and Turner, R. L. (1959): *Brit. med. J.*, **i**, 1315.
Wilkinson, J. F. (1955): 'Modern Trends in Blood Diseases', London, p. 235.

CURRENT THERAPEUTICS

CXLII.—THE NEWER STEROIDS

By MAUREEN SMITH, PH.D., HERBERT A. BURKE, JR., M.D., WILLIAM S. COPPAGE, JR., M.D., AND GRANT W. LIDDLE, M.D.

Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee

IN considering the potential therapeutic use of the newer steroidal agents we are reminded that 'one man's meat is another man's poison'. Practically all of the biologically active steroids have multiple biological effects. An effect which may be desirable in the treatment of one patient may be an undesirable side-effect prohibiting use of the agent in another patient. A corticosteroid having great activity in promoting sodium retention would be of considerable value in the management of Addison's disease but would not be acceptable in the treatment of rheumatoid arthritis, even though it possessed a fair degree of anti-inflammatory activity. A major effort of pharmaceutical chemists during the past few years has been to develop steroidal agents which are increasingly specific with regard to biological effects. Hopes and claims have sometimes outdistanced actual accomplishments; nevertheless, as a result of this effort the therapist has been provided with a variety of interesting new agents. Although the number of new steroidal agents which has been synthesized and tested must be counted in the hundreds, only a few of those which have had, or promise to have, an impact on clinical therapeutics will be considered in this short review (fig. 1).

NEW ANTI-INFLAMMATORY STEROIDS

With the advent in 1954 of prednisone and prednisolone (the 1-2 dehydrogenated analogues of cortisone and hydrocortisone, respectively) it became apparent that at least two major side-effects of the anti-inflammatory steroids, sodium retention and potassium wastage, could for all practical purposes be abolished. Consequently, as subsequent anti-inflammatory steroids were developed they were automatically rejected if the ratio of sodium-retaining to anti-inflammatory activity exceeded that of prednisone or prednisolone. Since 1954, increasing attention has been directed towards developing anti-inflammatory steroids which are free of diabetogenic, protein catabolic, or ACTH suppressive actions. The desired separation of these activities from anti-inflammatory activity has not been accomplished. Nevertheless, a number of interesting observations has been made concerning the relationship between the chemical configuration and the biological activity of corticosteroids.

It was found by Fried and Sabo, in 1953, that great enhancement of the biological activity of corticosteroids could be brought about by introduction

of a halogen atom into the 9α-position of the corticosteroid nucleus. Electrolyte-regulating activity was enhanced out of proportion to anti-inflammatory activity, and the early members of this series of compounds therefore were not acceptable in the clinic as anti-inflammatory agents. The significance

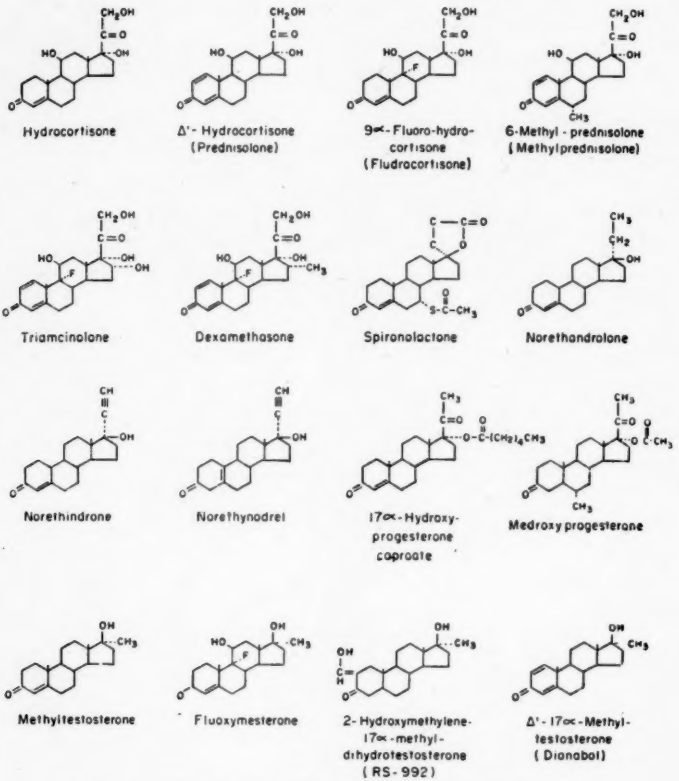


FIG. 1.—Chemical formulæ of some of the newer steroids.

of this discovery was not lost upon other workers, however, and many of the more recent anti-inflammatory steroids depend upon the presence of the 9α-fluorine configuration for their great biological activity.

In 1955, Herzog and his colleagues demonstrated that the anti-inflammatory activity of corticosteroids could be enhanced without concomitant enhancement of electrolyte-regulating activity by dehydrogenation of the corticosteroid nucleus in positions 1 and 2. This relative freedom from electrolyte side-effects gained for the 'Δ^1' compounds wide currency as anti-inflammatory agents. All of the corticosteroids which have come into general use as anti-inflammatory agents during the past five years

have been 1-2 dehydrogenated compounds. In 1956, Spero and his colleagues demonstrated that in many instances the introduction of a methyl group into the 6α-position of the corticosteroid nucleus had a definite influence on the biological activity of the compound. Only one member of the 6α-methyl series of corticosteroids, methylprednisolone, has been widely used as an anti-inflammatory agent. In this particular instance 6-methylation had little effect upon biological activity of the compound; 6-methylprednisolone has only slightly greater anti-inflammatory activity and slightly less sodium-retaining activity than prednisolone itself.

TRIAMCINOLONE AND DEXAMETHASONE

At about this point in the evolution of steroid pharmacology it became apparent that the tests which had been developed for assaying anti-inflammatory activity, carbohydrate-regulating activity, and electrolyte-regulating activity in rats could not be assumed to yield valid information concerning the biological activities of the synthetic corticosteroids in man. For example, 6-methyl-$\triangle^1$-9α-fluoro-21-desoxy-hydrocortisone was found to be approximately 135 times as potent as hydrocortisone as an anti-inflammatory agent in the rat, but it was found to be only about twice as effective as hydrocortisone as an anti-inflammatory agent in man (Liddle, 1958a). This sort of discrepancy between the animal assays and human assays has continued to plague steroid pharmacologists up to the present time. In 1956, Bernstein and his colleagues demonstrated that introduction of a hydroxyl group into the 16α-position of the corticosteroid nucleus almost totally abolished the electrolyte-regulating activity of the steroid while only moderately attenuating those properties associated with the anti-inflammatory activity of steroids. The most widely used member of this series, 16α-hydroxy-9α-fluoro-prednisolone, or *triamcinolone*, is approximately equal to prednisolone in its anti-inflammatory potency. According to some, triamcinolone differs from other anti-inflammatory steroids in being peculiarly effective in psoriasis. In addition to the usual metabolic side-effects of prednisolone it is said to produce the additional side-effects of anorexia and (when used in large dosages) marked muscular wasting and weakness (Dubois, 1958).

In 1958, Arth and his colleagues demonstrated that introduction of a methyl group into the 16α-position of the corticosteroid nucleus greatly attenuated electrolyte-regulating potency of the compound while increasing slightly the anti-inflammatory potency. The most widely used member of this series, 16α-methyl-9α-fluoro-prednisolone, or *dexamethasone*, is the most potent anti-inflammatory agent now available. It is approximately eight times as effective as prednisolone and approximately 30 times as effective as cortisone as an anti-inflammatory agent. Because of its great potency as an ACTH suppressing agent dexamethasone has recently been utilized in the development of a 'standard ACTH suppression test' in the diagnostic evaluation of patients suspected of having Cushing's syndrome (Liddle, 1959).

ELECTROLYTE-REGULATING STEROIDS

Because of the limited clinical application of steroids which possess prominent sodium-retaining and potassium-losing properties, there has been no great effort to develop agents of this type. Nevertheless, incidental to the effort to develop new anti-inflammatory agents, steroid chemists have developed a number of highly effective 'mineralocorticoids'. As already stated, the 9α-halogenated corticosteroids were in most instances found to be much more potent than their non-halogenated analogues with respect to their effects upon sodium and potassium excretion. 9α-fluoro-hydrocortisone, for example, is at least 125 times as effective as hydrocortisone in promoting sodium retention. This particular compound, under the name of *fludrocortisone*, has been made generally available for treatment of Addison's disease and 'salt-losing' congenital adrenal hyperplasia. It has the advantage of being fully effective when taken orally. Dosage of the order of 0.1 mg. once daily is adequate as an aldosterone substitute in most cases of adrenal insufficiency.

In 1955, Hogg and his colleagues developed the 2α-methyl series of corticosteroids, many of which were found to be extremely potent in their effects upon electrolyte metabolism. One of these compounds, 2α-methyl-9α-fluoro-hydrocortisone, was found to be over 3000 times as potent as hydrocortisone, 100 times as potent as desoxycorticosterone, and three times as potent as aldosterone. It remains the most effective sodium-retaining steroid yet described (Liddle *et al.*, 1956).

ALDOSTERONE ANTAGONISTS

In 1955, Landau and his colleagues demonstrated that progesterone tended to block the sodium-retaining action of deoxycortone. Following this lead, and with the additional knowledge that the potent adrenal hormone, aldosterone, played a role in the pathogenesis of œdema, Kagawa and his colleagues (1957) set out to develop a new series of steroidal agents, the 'spirolactones', which have as their characteristic property the antagonism of the biological actions of aldosterone and deoxycortone. Apart from blocking the effects of mineralocorticoids the spirolactones have little biological activity. The concept that the spirolactones exert their effects through the mechanism of aldosterone antagonism is supported by several lines of evidence (Liddle, 1958b).

(1) Spirolactones are effective only in the presence of the mineralocorticoids, exogenous or endogenous. Thus, in the patient with Addison's disease who is maintained solely by means of a high-salt diet the spirolactones have little effect on renal function, but when the same patient is maintained on a high-sodium diet plus deoxycortone, treatment with spirolactone results in a reversal of the characteristic effects of deoxycortone.

(2) The effects of the spirolactones are identical with those observed following acute withdrawal of aldosterone. Whereas aldosterone causes a decrease in urinary sodium, chloride and volume, the spirolactones bring about an increase in urinary sodium, chloride and volume. Whereas aldosterone causes an acute increase in urinary potassium, titratable acidity and ammonia, the spirolactones bring about an acute decrease in urinary potassium, titratable acid and ammonia.

(3) Available evidence indicates that the actions of spirolactones cannot be explained in terms of any effect upon glomerular filtration rate or upon adrenocortical synthesis of aldosterone.

One of these compounds has been made generally available under the name of 'spironolactone' for use as a diuretic and anti-hypertensive agent. Although spironolactone is rarely a spectacular diuretic agent, it is often very useful as an adjunct to conventional diuretics in œdematous patients who have become refractory to the conventional agents. Spironolactone has

Compound	Relative potency	Usual anabolic dose mg. per day
Methyltestosterone	1	20
11*b*-Hydroxy-methyltestosterone	1-2	10-20
Fluoxymesterone	3	5
Dianabol	8	2-3
RS-992	3	5-10
Norethandrolone	1-2	10

TABLE I.—Relative anabolic potency of various testosterone derivatives administered orally to human subjects.

the unique property of augmenting sodium excretion while diminishing the excessive potassium excretion which is commonly seen with conventional diuretic therapy.

ANABOLIC STEROIDS

For several years there has been a search for a steroid which would promote protein anabolism without causing virilism. Repeatedly compounds have been developed which, in the rat, have shown dissociation of anabolic activity from androgenic activity in favour of the former. Such a dissociation of biological effects has rarely been observed, however, when these compounds have been used clinically. Since the virilizing properties of steroids are very difficult to assay in human subjects there has often been a lag between the recognition that a new steroid is a potent anabolic agent and the recognition that it is a potent androgenic agent as well. Most endocrinologists have become very cautious about claiming a dissociation of these effects. The one compound which has been widely used during the past three years and for which there appears some justification for claims of partial dissociation of anabolic activity from androgenic activity is norethandrolone. It is undeniable that norethandrolone is an androgenic steroid, but there are many who feel that if dosage is kept low this agent has relatively little virilizing activity per unit anabolic activity when compared with, say, methyltestosterone.

Quite apart from the question of proving dissociation of anabolic activity from androgenic activity, there is the difficult task of performing valid assays of anabolic activity in man. Recently a deliberate attempt has been made to perform such assays in an effort to correlate chemical structure with biological potency of certain testosterone analogues (Burke and

Liddle, 1959). Preliminary observations have suggested that several of the newer analogues of testosterone are more effective when administered orally than is the older standard preparation, methyltestosterone. Relative metabolic potencies of some of these compounds are indicated in table I. From these studies it appears that we must remain flexible in our thinking about the relationships between chemical structure and biological effectiveness of the anabolic steroids. It is highly interesting that 4-5 unsaturation is not essential for biological activity of anabolic steroids; that 1-2 dehydrogenation potentiates the biological activity of certain anabolic steroids as well as the catabolic corticosteroids; and that 11-oxygenation does not invariably decrease the anabolic activity of steroids.

One disadvantage of the new testosterone analogues is that in some instances they appear to cause mild derangements of hepatic function when used in large dosages over long periods of time (Kory *et al.*, 1959).

NEW PROGESTATIONAL STEROIDS

The search for a synthetic progestational agent of high potency, lacking in side-effects and preferably active when administered orally, has led to the synthesis of a number of effective compounds belonging to two main groups: derivatives of progesterone itself and derivatives of 19-nortestosterone.

The most widely used of the progesterone derivatives have been 17α-hydroxyprogesterone-17-*n*-caproate and 6α-methyl-17α-hydroxyprogesterone acetate (medroxyprogesterone). It has been known for some time that esterification of steroid hormones often prolongs their duration of action, but it was surprising to find that the caproate of 17α-hydroxyprogesterone was not only longer-acting but also much more potent as a progestational agent than its parent compound (Junkman, 1954). A single intramuscular injection of 250 to 500 mg. sustains a secretory endometrium in œstrogen-primed castrate women for 7 to 17 days followed by withdrawal bleeding. Medroxyprogesterone is an even more potent progestational agent (Greenblatt and Barfield, 1959) and has the additional advantage of being effective after oral administration. Dosage of 2 to 5 mg. for five days leads to withdrawal bleeding in over 75 per cent. of castrate or amenhorrœic women in the presence of adequate œstrogen. The most widely used of the 19-nortestosterone derivatives are 17α-ethyl-19-nortestosterone (***norethandrolone***), 17α-ethinyl-19-nortestosterone (***norethindrone***), 17α-ethinyl-19-nortestosterone enanthate, and 17α-ethinyl-5(10)-œstrænolone (***norethynodrel***). Although norethandrolone is a fairly potent progestational agent, oral doses of 10 to 15 mg. a day producing a secretory endometrium in œstrogen-primed castrate women, its use as such is vitiated by its androgenic activity.

Norethindrone and norethynodrel are both very potent progestational agents (Greenblatt, 1956; Epstein *et al.*, 1958), oral doses of 10 mg. a day causing withdrawal bleeding two to five days after cessation of therapy in

essentially all castrate or amenorrhœic women. These compounds do not necessarily require concomitant œstrogen administration for effectiveness, although the addition of œstrogen reduces the incidence of break-through bleeding. Indeed, norethynodrel has 3 to 7 per cent. of the œstrogenic activity of œstrone, a property which is thought to be conferred by the 5-10 double bond. The enanthate of norethindrone is a long-acting parenteral progestational agent, a single 50 to 150 mg. intramuscular injection providing full replacement and causing withdrawal bleeding as long as 16 to 28 days after therapy in the œstrogen-primed surgical castrate. It is the most potent and longest acting progestational substance presently available for parenteral administration.

Apart from the regulation of menstrual cycles in patients with amenorrhœa, these compounds are of use in a variety of menstrual disorders such as functional uterine bleeding, in which norethindrone and norethynodrel are particularly useful. Doses of 10 to 30 mg. a day diminish profuse bleeding in several hours and arrest it completely in twenty-four to forty-eight hours (Southam, 1958). The ability of these two compounds to suppress menstruation indefinitely in doses of 40 mg. a day is of use in treating endometriosis (Kistner, 1958).

There is considerable indirect evidence—from basal temperature curves, cervical and vaginal smears, pregnanediol excretion, and endometrial biopsies—that norethandrolone, norethindrone, and norethynodrel will inhibit ovulation (Rock *et al.*, 1957). The precise mechanism is not clear; the possibility that they act through suppression of pituitary gonadotrophins has not been excluded. Large-scale studies of the use of these compounds as oral contraceptives are now being carried out (Garcia *et. al.*, 1958; Tyler and Olson, 1959), and preliminary results are promising.

The use of progestational steroids in habitual and threatened abortion has been advocated and fairly widely practised, but it is difficult to find a large, properly controlled series of cases for the purpose of evaluating the efficacy of this method of treatment (Reifenstein, 1958). An occasional complication of such therapy has been emphasized by Wilkins *et al.* (1958), who have accumulated a series of cases in which some degree of pseudohermaphroditism has occurred in female infants whose mothers received large quantities of progestational steroids during pregnancy.

CHOLESTEROL-DEPRESSING STEROIDS

The realization that the comparative immunity of the premenopausal women from atherosclerosis was largely attributable to high levels of endogenous œstrogens has led—so far with little success—to a search for a synthetic substance having similar effects in lowering plasma cholesterol and altering the serum lipid pattern but without the feminizing effects of the œstrogens. The simultaneous administration of both œstrogen and androgen has proved disappointing in that the cholesterol-lowering effect of the œstrogen seems to be abolished without altering its feminizing

effects. One synthetic compound which gave promising results in animals is mytatrienediol, but it has proved more œstrogenic than expected in man (Davis *et al.*, 1958; Cohen *et al.*, 1959). Doses large enough to cause favourable lipid shifts in 50 per cent. of the atherosclerotic men tested, i.e. doses greater than 20 mg. a day for several months, also caused loss of libido and/or breast tenderness and enlargement in 50 per cent. of cases.

A new field for research has been opened up by the recent observation (Hellman *et al.*, 1959) that androsterone (a normal metabolite of the naturally occurring androgens, testosterone and androstenedione) is effective in lowering serum cholesterol levels when given in doses of 50 mg. a day intramuscularly. The conversion of testosterone to androsterone is apparently influenced by the thyroid, more androsterone being produced under the influence of exogenous tri-iodothyronine and in hyperthyroid subjects and less being produced in hypothyroid subjects. This observation is of interest not only in demonstrating one mechanism through which thyroid hormones control serum cholesterol but also in suggesting a new class of potential synthetic cholesterol-depressing agents.

The original studies referred to in this article were supported in part by grants-in-aid from the U.S. Public Health Service (CY-3107 and 2A-5092) and the John A. Hartford Foundation, Inc.

References

Arth, G. E., *et al.* (1958): *J. Amer. chem. Soc.*, **80,** 3161.
Bernstein, S., *et al.* (1956): *Ibid.*, **78,** 5693.
Burke, H. A., Jr., and Liddle, G. W. (1959): 'Proceedings of The Endocrine Society', p. 45.
Cohen, W. D., *et al.* (1959): 'Hormones and Atherosclerosis', New York, p. 443.
Davis, F. W., *et al.* (1958): *Amer. J. med. Sci.*, **235,** 50.
Dubois, E. L. (1958): *Metabolism*, **7,** 509.
Epstein, J. A., *et al.* (1958): *Ann. N.Y. Acad. Sci.*, **71,** 560.
Fried, J., and Sabo, E. F. (1953): *J. Amer. chem. Soc.*, **75,** 2273.
Garcia, C. R., Pincus, G., and Rock, J. (1958): *Amer. J. Obstet. Gynec.*, **75,** 82.
Greenblatt, R. B. (1956): *J. clin. Endocr.*, **16,** 869.
——, and Barfield, W. E. (1959): *South. med. J., Bgham, Ala*, **52,** 345.
Hellman, L., *et al.* (1959): *J. clin. Endocr.*, **19,** 936.
Herzog, H. L., *et al.* (1955): *Science*, **121,** 176.
Hogg, J. A., *et al.* (1955): *J. Amer. chem. Soc.*, **77,** 6401.
Junkman, K. (1954): *Arch. exp. Path. Pharmak.*, **223,** 244.
Kagawa, C. M., Cella, J. A., and Van Arman, C. G. (1957): *Science*, **126,** 1015.
Kistner, R. W. (1958): *Postgrad. Med.*, **24,** 505.
Kory, R. C., *et al.* (1959): *Amer. J. Med.*, **26,** 243.
Landau, R. L., *et al.* (1955): *J. clin. Endocr.*, **15,** 1194.
Liddle, G. W. (1958a): *Metabolism*, **8,** 405.
—— (1958b): *A.M.A. Arch. intern. Med.*, **102,** 998.
—— (1959): 'Progress in Clinical Endocrinology', 2nd ed., New York (in the press).
——, Richard, J. E., and Tomkins, G. M. (1956): *Metabolism*, **5,** 384.
Reifenstein, E. C., Jr. (1958): *Ann. N.Y. Acad. Sci.*, **71,** 560.
Rock, J., Garcia, C. R., and Pincus, G. (1957): *Rec. Progr. Hormone Res.*, **13,** 323.
Southam, A. L. (1958): *Ann. N.Y. Acad. Sci.*, **71,** 666.
Spero, G. B., *et al.* (1956): *J. Amer. chem. Soc.*, **78,** 6213.
Tyler, E. T., and Olson, H. J. (1959): *J. Amer. med. Ass.*, **169,** 129.
Wilkins, L., *et al.* (1958): *J. clin. Endocr.*, **18,** 559.

PRACTICAL DIETETICS

X.—DIETS IN GASTROENTERITIS IN INFANTS AND YOUNG CHILDREN

By M. J. O. FREEMAN, S.R.N., Dipl. in Dietetics
Chief Dietitian, Royal Victoria Infirmary, Newcastle upon Tyne

Diet as a curative measure in gastroenteritis has, of course, been largely superseded by antibiotic therapy, and the present diet therapy is designed to be used in conjunction with this. Initially the diet copes with providing calories for basal metabolism; it then aims at avoiding irritation of the bowel, and finally at providing a nourishing acceptable diet.

A constant awareness of the danger of dehydration is essential. No restriction should be placed on the fluid intake. It is easy to make drinks calorific and quickly assimilable by the addition of glucose, which should be utilized whenever possible.

The dietary pattern of treatment for gastroenteritis in infants and young children is generally in three stages.

INITIAL STAGE

The diet in the initial stage is designed to restore fluid and sodium balance within the body, and restore to normal the pH and bacterial flora of the intestinal tract. It must also be remembered that the child feels very ill and the essential foods must be given in an easily assimilable, palatable way.

Infants.—Water only is given for the first twenty-four hours; quarter-strength feeds for the next twenty-four hours; half-strength feeds for the next twenty-four hours, and then normal-strength feeds. The length of time at each stage naturally depends upon the child's rate of recovery.

Children being weaned.—Water only for twenty-four hours. Normal bottle feeds being given (i.e. one or two a day) should be continued at reduced strength as above. Between these the solid part of the child's diet should consist of: (a) raw grated apple; (b) fruit juice (of the type to which the child is accustomed) to which is added extra sugar.

Young children.—Small but regular feeds of raw grated apple (up to a pound [0.45 kg.] a day is not excessive). Yoghourt (well-sweetened to be acceptable to a child's palate) plus blackcurrant purée. Yeast extract drinks. Pure fruit juices with added sugar or glucose. Partially skimmed milk.

This means giving a high-calorie, high-vitamin diet which, when taken with the apple, which has an anti-diarrhœic effect, is of most value to the child.

SECOND STAGE

The diet in the second stage is one that is low in residue, and also designed essentially to tempt the appetite and prepare the way for necessary rebuild-

ing, while also avoiding irritation in the bowel. A sample day's menu is given below. The importance of all foods being absolutely fresh should be stressed.

Breakfast:	Milk (cream removed) Strained orange juice Fine oatmeal porridge *or* cornflakes *or* Rice Krispies Crustless bread and butter Toast (which should be buttered when cold) Jelly marmalade, honey, lemon curd
Mid-morning:	Yoghourt, sugar and sieved fruit Blackcurrant drink
Midday:	Thick sieved vegetable soup (home-made if possible) Tinned soup should be thinned with milk Small portion of minced meat *or* tender roast meat *or* grilled lean bacon *or* ham *or* baked or steamed fish Serve the meat or fish with mashed or young boiled potatoes and sieved vegetables. These assist in adding the necessary bulk and calories Pudding—jelly, apple snow, milk pudding, egg custard
Tea:	Weak milky tea or milk shake (flavoured milk and ice-cream) Crustless white bread and butter Jelly jam, honey, syrup Plain cake without currants or coconut Plain or chocolate biscuits

THIRD STAGE

Here particular attention should be paid to a high calorie, high vitamin content, but nothing should be given to the child which he has previously disliked. In order not to aggravate the bowel, no roughage (i.e. coarse wholemeal bread or biscuits, oranges, soft fruits, tomatoes, cabbage) should be allowed. The main essentials are to provide the child with a well-balanced diet made up from the foods for which he has a preference, but yet not to encourage faddism at the expense of undernutrition. With infants and young babies the only course open after the initial stage is to return to their normal diet as soon as possible and not to introduce any new foods to the dietary until the child is fully recovered. The following is a diet suitable for a child aged 2 to 5 years:

On waking:	4 fluid ounces (114 ml.) orange juice
Breakfast:	5 fluid ounces (142 ml.) milk 4 fluid ounces (114 ml.) porridge or cereal 1 egg or 1 ounce (28.5 g.) bacon 1 ounce (28.5 g.) bread and butter ½ ounce (15 g.) sugar
Mid-morning:	5 fluid ounces (142 ml.) milk
Dinner:	2 ounces (57 g.) mince or fish 2 ounces (57 g.) potatoes 2 ounces (57 g.) vegetable (sieved at first after gastroenteritis) 5 ounces (142 g.) milk pudding *or* fruit and custard *or* jelly and custard
Tea:	5 fluid ounces (142 ml.) milk 1 ounce (28.5 g.) bread and butter Jam and sugar 1 ounce (28.5 g.) cheese or egg Fruit
Bedtime:	5 ounces (142 ml.) milk

The portions must be regulated to suit the individual needs of the child. Milk, eggs, cheese, meat, cereals, green vegetables and fruit should figure in the diet so far as possible. Sweets, chocolate and biscuits should be given at the end of a meal.

RECIPES

High-protein milk supplement:—

2 egg-whites
4 tablespoonsful dried skimmed milk
2-3 teaspoonsful sugar
Two-thirds cup milk

Beat egg-whites stiffly but not dry, add sugar and dried milk, mix well and combine with milk mixture. The nutritional content of this high-protein milk supplement is as follows:—

	Carbohydrate (g.)	Protein (g.)	Fat (g.)
2 fluid ounces (57 ml.) skim milk	27.2	20.4	0.4
1 ounce (28.5 g.) sugar	30.0	—	—
2 egg whites	—	5.2	—
5 fluid ounces (142 ml.) milk	6.0	5.0	5.0
Total nutritional content	63.2	50.6	5.4

Baked fish can be rolled, covered with crushed cornflakes, milk and greaseproof paper and cooked in a moderate oven. It may also be cooked in an unsweetened egg custard mixture.

Steamed fish is more readily eaten by children if it is coated with a home-made tomato sauce. Make this by adding fresh or tube tomato purée to a plain white sauce.

Sieved vegetables.—Only carrots, turnips, parsnips and cauliflower can be sieved successfully at home (unless a homogenizer is available) but tins of various very good sieved vegetables are available at a reasonable cost.

Jelly (always acceptable) preferably made at home with:—

½ pint lemon juice and water or diluted Government orange juice
½ ounce gelatin dissolved in warm water
2 tablespoonsful sugar as desired

Milk jelly.—Packet jelly made up with milk.

Russian jelly.—Packet jelly dissolved in water, allowed almost to set and then whisked into previously whipped evaporated milk.

Apple snow.—One whipped egg-white (stiffly beaten) folded into 3 ounces (85 g.) of sieved cooked apple. Serve uncooked with a plain shortbread biscuit.

Milk puddings of the duller variety are more tempting to a child's palate if one egg yolk per half-pint (285 ml.) of mixture is stirred in and then a whipped egg-white folded in during the final quarter-hour of baking.

Egg custard-chocolate.—Dissolve some drinking chocolate in the milk from which the pudding is to be made. Cook in the usual way. Decorate with grated chocolate. Cream may be added.

REVISION CORNER

SEA-SNAKE BITE AND POISONING

THE title of this article is chosen to emphasize that sea-snake bite and poisoning are by no means synonymous. Sea-snakes are common in river-mouths and shallows of the Indian and Pacific Oceans. One species ranges as far as the western coasts of America and eastern coasts of Africa. Over fifty species are described. Length varies from one to ten feet (30 cm. to 3 metres), thickness from a pencil to that of a man's thigh but commonly they are three feet (0.9 metres) long and the thickness of an adult toe (fig. 1). All sea-snakes secrete highly toxic venom and have small fixed fangs (2 to 3 mm. long) corresponding to human canine teeth. They are easily distinguished from land- and water-snakes by their flat, rudder-like tail (water-snakes have round tapering tails and are also common in coastal waters but are harmless to humans). Sea-snakes have valved nostrils enabling expiration under water but have to surface to inspire. They are swift and graceful swimmers, feeding on a variety of fish, mostly on the sea-bed.

THE RISK OF SEA-SNAKE BITE

Bathers are occasionally bitten when they inadvertently tread on sea-snakes. Usually the risk is greatly exaggerated—it has been statistically assessed at one bite per 270,000 man bathing hours. In Penang Island waters during 1955-58, 17 bathers died from accidental drowning and only two from sea-snake bites. Venomous fish-stings among bathers were over eight times more common than sea-snake bites. Provided the sea-bed is not touched, the risk of bites is negligible. To fishermen, however, sea-snake bite is an occupational hazard and in north-west Malaya during 1955-58 some 40 victims were admitted each year. Many fishing folk did not come to hospital (Reid and Lim, 1957) and therefore these figures do not reflect the true incidence of sea-snake bite.

The risk of toxæmia.—After the initial prick, the site of a sea-snake bite does not become swollen or painful—in contrast to fish-stings which are extremely painful. One, two or more pin-head sized dots from fangs (and teeth) momentarily ooze blood. In the majority of victims *no symptoms of poisoning ensue*—because insignificant venom is injected. In a minority (not more than 30 per cent.) symptoms of toxæmia become evident one-half to one hour after the bite.

PATHOLOGY

Absorption of sea-snake venom is rapid. It passes up the subcutaneous tissues and lymphatics of the bitten limb within a few minutes, thence to the pulmonary circuit and then into the systemic circulation. In human victims sea-snake venom is primarily myotoxic, attacking skeletal muscle. Pathologically the principal lesions are widespread necrosis of skeletal

muscle, tubular necrosis of the kidneys and toxic centri-lobular changes in the liver.

CLINICAL PICTURE OF TOXÆMIA

The first symptom of sea-snake bite poisoning is muscle movement pain in the neck or proximal limbs one-half to one hour following the bite. This aching stiffness becomes generalized after ten to fifteen minutes. Initially

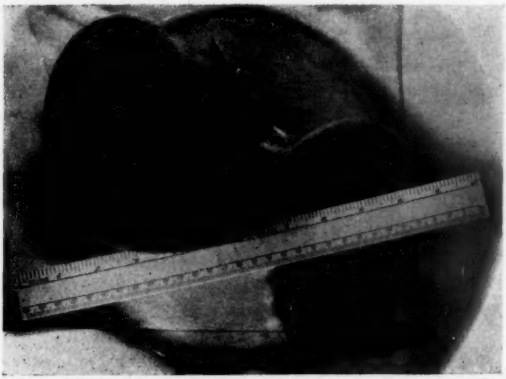


FIG. 1.—*Enhydrina schistosa* Daudin the most common species of sea-snake. The back is uniform grey, the belly white, but most other species are banded. Note the typical flattened rudder-like tail which distinguishes poisonous sea-snakes from harmless water-snakes.

it is like the muscle soreness after unaccustomed exercise. As severity increases the victim is unwilling to move on account of the pain (and this is usually mistaken for paresis). Passive flexion of limbs and spine is strongly resented. Difficulty in moving the lids, eyes, face, jaw, tongue and pharynx develops an hour or so later in severe cases. Involvement of jaw muscles leads to pseudo-trismus—a splinting effect of intact muscle cells protecting the damaged ones. After some hours, true paresis of peripheral type may ensue and, later still, tendon reflexes become depressed then absent. Other early features are constant thirst, episodic sweating and vomiting. Some three to eight hours after the bite the urine becomes positive for albumin and occult blood. Within half-an-hour myoglobinuria is visible, the colour changing to brown or red-brown. In most cases the blood pressure is normal. Sometimes there is early hypertension—probably secondary to nephrotoxic effects —but usually this is a late development of asphyxial origin.

In victims destined to die (only about 5 per cent. of those bitten) respiratory failure may supervene within a few hours of the bite or as long as sixty hours after the bite. The subject becomes drowsy then comatose. Pupils dilate and their reaction to light fails shortly before death. Other patients succumb from hyperkalæmic cardiac arrest, acute renal failure or general metabolic toxæmia. Three-quarters of the victims dying do so

within twenty-four hours of the bite. The most rapid death recorded is 2½ hours after the bite, the most protracted is twelve days.

Recovery in a severe case may take up to six months. Myalgia and myoglobinuria reach a peak during the first week and recede early in the second week. Paresis becomes more complete during this week. Improvement in power starts slowly during the third week. Tendon reflexes return during the third or fourth week. The patient is now able to lift his head off the bed and sits up by rolling on to his side and helping himself up with his arms. For the next month the clinical resemblance to muscular dystrophy is striking—the patient 'climbs up himself'. During the following few months hand-grip, 'press ups' and sitting up spontaneously from the lying position slowly return to normal. Full recovery occurs in three to four weeks in moderate cases; within a few days in trivial poisoning.

If significant toxæmia follows a sea-snake bite, moderate leucocytosis is invariable. The degree and duration correlate approximately with the severity of the toxæmia. Hæmoglobin is normal or increased. There is no evidence of abnormal hæmolysis or coagulation defect. Myoglobinuria can be distinguished from hæmoglobinuria by a hand spectroscope using fluorescent lighting (Bowden *et al.*, 1956). Acute renal failure may be present during the first few weeks in severe cases and follow-up studies two to three years after the bite indicate that the kidneys may be permanently damaged. No evidence of long-term damage to muscle, nerve or liver tissue was found.

DIAGNOSIS

Diagnosis is important when the sea-snake has not been reliably recognized, which is usual with bathing victims. In such cases, local pain following the bite excludes a sea-snake bite (and confirms a fish-sting). If no local pain followed, the vital question arises—has significant envenomation occurred? If an hour has elapsed since the bite and the patient feels no *generalized* muscle movement pains, significant toxæmia can be excluded—and whether or not it was a sea-snake is of mere academic interest. The exception to this 'one-hour clearance' is the rare instance when an effective tourniquet was applied within a minute or two of the bite and not released when first seen by the doctor.

TREATMENT

In considering appropriate treatment it is essential to remember:—

(1) The majority of human victims will not have significant venom injected and therefore only require adequate reassurance.

(2) In the minority receiving significant envenomation, absorption is rapid —a matter of a few minutes. By the time this unfortunate minority presents to a doctor it is far too late for local measures, such as ligature, incision or excision, to be of any benefit to the patient. Confusion between first-aid measures theoretically effective within a few minutes of the bite and medical treatment is unfortunately common in articles dealing with snake-bite treatment. A doctor, however, may be asked the general question: How can one

avoid sea-snake bites and what should one do if bitten? If bathers keep swimming the risk is negligible. If one is bitten, tie a ligature round the toe or thigh, leave the bite-mark alone and come to hospital with the minimum physical exertion and maximum speed possible.

When first seen by a doctor, the majority will pass the 'one-hour clearance' test and the most adequate reassurance is a placebo intramuscular injection of 'imferon'. If, however, significant toxæmia is apparent, treatment then falls into three categories: (1) removal of poison from the body; (2) antidotes (chemical and physiological); (3) supportive treatment. Removal of sea-snake venom locally from the site of the bite is not feasible as hospital treatment. Renal excretion and renal protection should be promoted by persuading the patient to drink a litre of water as quickly as possible. More effective is a rapid intravenous infusion of a litre of 25 per cent. glucose, 10 per cent. calcium gluconate and molar sodium lactate. The chemical antidote—an effective sea-snake antivenene—is not yet available although the Commonwealth Serum Laboratories in Melbourne are undertaking production with venom from the Sea-snake and Venom Institute, Penang. Land-snake antivenenes are ineffective, sometimes harmful. Physical rest is the most important physiological antidote. It minimizes damage to the sarcolemmal sheaths which guide regenerating skeletal muscle. In severe cases postural treatment to prevent inhalation of vomit or secretions is needed during the first few days. Steroid therapy may be given as a non-specific anti-toxæmic drug and as a means of increasing renal excretion of potassium although its practical value, in my experience, is doubtful. Respiratory failure is best treated by tank respirator (tracheostomy and intermittent positive-negative pressure artificial respiration have proved disappointing). Hyperkalæmia may be diagnosed by serial electrocardiograms, and insulin should be given if tall peaked T waves appear. After the first twenty-four to forty-eight hours, acute renal failure is the main danger. If urine specific gravity becomes 'fixed', treatment as described by Bull (1958) is indicated. If the twenty-four-hour output falls to below 500 ml. the outlook is grave, but in the tropics a daily fluid allowance of 700 to 1000 ml. rather than 500 ml. is indicated in view of the greater sweat loss.

PROGNOSIS

Multiple bite-marks suggest a high venom dose (but single marks do not necessarily indicate a small dose). Vomiting, ptosis, weakness of external eye muscles, dilatation of pupils with a sluggish light reaction and a leucocytosis exceeding 20,000 per c.mm. are all sinister signs. If the patient survives the first week, recovery may be predicted although it may take weeks or months. Each day myoglobin is visible on inspecting the urine means approximately one week of illness.

SUMMARY

(1) The risk to bathers of sea-snake bite is remote: to fishing folk it is an occupational hazard.

(2) Although sea-snake venom is highly toxic only one-third of human victims develop significant toxæmia.

(3) In these, generalized muscle movement pains and myoglobinuria are the outstanding clinical features. Appropriate treatment is summarized.

This article is based on recent work, details of which will be published elsewhere.

H. A. REID, M.B., F.R.C.P.ED., D.T.M. & H.
Physician, General Hospital, Penang.

References

Bowden, D. H., Fraser, D., Jackson, S. H., and Walker, N. F. (1956): *Medicine (Baltimore)*, **35**, 335.
Bull, G. M. (1958): *The Practitioner*, **181**, 262.
Reid, H. A., and Lim, K. J. (1957): *Brit. med. J.*, **ii**, 1266.

NOTES AND QUERIES

Steroid Treatment of Asthma in Childhood

QUERY (from a reader in Malta).—For some months now I have been treating my child asthma patients with triamcinolone which is said to have less side-effects than prednisone or prednisolone. The results have been excellent. I have based my treatment on a report by Maxwell, of Melbourne, Australia, who advises prolonged therapy (about two years) with adrenocortical hormones. The dose, naturally, varies with the age and response of the patient but on the average it is one tablet a day in divided doses (4 mg.). Because of the possible atrophic effect on the adrenal cortex, a seven-day course of 10 to 20 units daily of corticotrophin is given every 1 to 2 months.

Although the results have been more than satisfactory (not one patient has had an attack since starting treatment), a careful check is kept to exclude harmful effects. The patient is seen once every ten days and a careful note is kept on his weight, urinary output, and muscle weakness or fatigue, and an eosinophil count is also carried out.

I would like an authoritative opinion on the advisability of carrying out such treatment in infants aged 6 months and over who have repeated attacks and who have failed to respond to other remedies. Provided a careful and regular check is kept on the infant, including a regular eosinophil count, is there any reason why this effective therapy should not be extended to young infants?

REPLY.—In this country general opinion is against the use of long-term adrenal corticosteroids in asthma, except in the most severe cases. This means that this use should be limited to those in whom repeated attacks of status asthmaticus occur, or whose life is seriously restricted by their asthma, and not merely because of frequent attacks which cannot be controlled by bronchodilator drugs. In children interference with development would be an adequate reason for consideration of their use. Nevertheless, it must be remembered that steroid therapy, in addition to its other side-effects, may inhibit growth in childhood.

Suppression of the suprarenal cortex by even small doses of steroid when administered for six months or more renders patients so treated liable to sudden collapse under conditions of stress such as anæsthesia or accident, and this risk persists for a number of months after steroid therapy has been discontinued. Even intermittent injections of corticotrophin do not necessarily prevent this effect.

Silent infection is at least as great a risk in children as in adults; it is also by no means easy to wean the successfully treated patient from steroids. Short-term therapy in severe attacks is less likely to produce these serious effects, and even if employed repeatedly is preferable to their continued use. The same rule

applies in infants as in older children, but there is no contraindication to the use of steroids provided the severity of the disease justifies their use. The newer steroids, including triamcinolone, have some advantage in that they are not so liable to cause œdema and increase in weight, but triamcinolone is best avoided because of the very real risk of muscle wasting and weakness which is associated with it.

It must be remembered that death from asthma is rare in children compared with those whose asthma starts after the age of 40, and this fact must be taken into consideration in deciding whether to use steroids in treatment.

R. S. BRUCE PEARSON, D.M., F.R.C.P.

Alcohol and Driving

QUERY.—(1) What is the percentage of blood alcohol that has been deemed safe in the case of a car driver?

(2) How much do the blood levels of alcohol vary from hour to hour, the person having ceased to consume any further alcohol?

REPLY.—(1) The percentage of alcohol in the blood which the B.M.A. Committee regards as *the maximum* commensurate with safe driving is 0.15%. This does not, of course, mean that everybody is safe at this figure; in fact, Drew's work has shown that at very much lower figures many drivers are appreciably affected to some extent. On the other hand, there is little doubt that with considerably higher figures some people show no evidence of deterioration on *clinical examination*. Again, however, it seems that many people's driving skill is, in fact, impaired even though they can pass clinical tests.

(2) The change in the blood level after cessation of consumption will depend upon certain factors, the most obvious being that, although a person has ceased to drink, he may still have alcohol in his stomach which will be absorbed later. The maximum level in the blood, however, will be achieved somewhere between a half to one hour after consumption. Once all the alcohol is absorbed, then the blood percentage will drop at a fixed rate of about 0.015 mg. % per hour.

F. E. CAMPS, M.D., D.T.M. & H.

Liquid Nitrogen and Warts

QUERY.—What are the indications for the use of liquid nitrogen in the treatment of warts in general practice? How should it be used?

REPLY.—There are no specific clinical indications for the use of liquid nitrogen in the treatment of warts; the fluid can be used for the treatment of any common wart in which refrigeration may reasonably be expected to be of benefit but, because the liquid is intensely cold, most prefer to use it for small warts which rapidly thaw after freezing and not for large indurated lesions which have to be deeply frozen for relatively long periods with a consequent risk of severe tissue necrosis. Used carefully, liquid nitrogen is satisfactory for the treatment of common warts adjacent to the nails as well as for those elsewhere on the hands. Very light refrigeration can be used for the treatment of plane (juvenile) warts: small plantar warts can be treated with liquid nitrogen but require somewhat longer periods of refrigeration than common warts. For comparison it may be of interest to note that carbon dioxide 'snow' has a temperature of −79°C., liquid oxygen (which can be used in the same way as liquid nitrogen) −183°C., and liquid nitrogen −195.8°C. None of these gases has any therapeutic properties; their virtue lies solely in their coldness.

Liquid nitrogen and oxygen are obtained in relatively large amounts (half a pint [280 ml.] or more) from the manufacturers. Special containers may be available, but they can be collected and stored in ordinary household thermos flasks: no ordinary flask will retain liquid oxygen or nitrogen for more than a few days. Because the liquid has to be bought in relatively large amounts it is wasteful to obtain a supply for only one case. Half a pint of liquid nitrogen is more than enough for the treatment of 200 warts. To avoid serious accidents, flasks containing liquid gases should be kept well out of reach of patients, and (for they are easily tipped over) are best kept standing in well-fitting heavy wooden bases.

For use a small amount of cotton wool is rolled tightly on to the end of a thin cylindrical wooden applicator (e.g. an orange stick). The wool is dipped in the liquid in the flask and at once gently pressed on to the wart. Almost immediately the whiteness of frost-bite can be seen in the tissue. The area and an areola of 1 to 2 mm. is kept frozen for a suitable period, depending upon the size and thickness of the lesion. From time to time the operator quickly dips the wool into the nitrogen and reapplies it to the wart so that the temperature is maintained. A small common wart may require freezing only for seven to ten seconds; a wart ½ cm. in diameter fifteen to thirty seconds. It is only when a good deal of experience has been gained that the operator should contemplate treatments of more than thirty seconds. Often there is less immediate pain, thawing pain and blistering than when carbon dioxide is used. In many instances the treated area is only slightly swollen and painful for forty-eight hours, then the wart dries up,

becomes brown and hard, and after about twenty-one days peels off. Therefore if the first attempt does not appear to have been successful, at least three to four weeks should elapse before the wart is frozen again and for a longer period.

R. M. B. MACKENNA, M.D., F.R.C.P.

Twitching Eyelids

QUERY.—A patient of mine has had a twitching in her right lower eyelid for over a year. The twitching is involuntary, constant and can be observed on careful inspection. Sedatives have not helped. I would be grateful for expert views on the cause of this condition and for advice on treatment.

REPLY.—Twitching in the lower eyelid, *with no other signs*, often referred to by the laity as 'live blood', is usually a sign of nervous exhaustion associated with overwork and worry and occasionally of eye strain, especially due to uncorrected errors of refraction. It is unusual for it to last for a year. It would be interesting to know whether in fact it has been continuous or merely recurrent over the year, which is much more common. Correction of any fault in refraction and a good holiday will usually stop the annoying symptom. Sedatives are quite useless

A. H. DOUTHWAITE, M.D., F.R.C.P.

Gold Sensitivity

QUERY.—I would be most grateful for advice in the following problem. The patient is a young woman aged 24 years. She wore gold bracelets and necklaces from adolescence, and a gold wedding ring for about three months of marriage, by which time she was two months pregnant. She then developed a weeping, bleeding eczematous reaction beneath her wedding ring. After a brief trial of topical hydrocortisone, which gave relief at the time but no lasting benefit, the ring was abandoned for the remainder of the pregnancy. Following delivery several attempts have been made to wear the wedding ring and other gold jewellery. After a short time (two to three hours) itching, erythema, and later eczema with bleeding develop in relation to the gold objects. It is now seven months since delivery of a healthy boy.

I presume the diagnosis to be gold sensitivity, induced by pregnancy and persistent after delivery. The patient also demonstrates mild sensitivity—itching and erythema—to certain detergents and 'dettol' solutions, but has no history of other allergies.

Please advise on the following aspects:—

(1) What is the natural history of this condition?

(2) What treatment is recommended?

(3) If desensitization is feasible, is it worth while in these cases?

(4) Are there any hazards of therapy, bearing in mind the unpleasant consequences such as exfoliative dermatitis which occasionally follow gold therapy?

(5) Would the wisest course be to accept the gold allergy and to change to an alternative precious metal for personal adornment?

REPLY.—This query raises several points which are of interest in the problem of sensitization dermatitis. First of all, sensitization of the skin to contact with gold jewellery is very uncommon and before making a confident diagnosis of 'gold sensitivity' the patient should be patch tested, using 2% gold chloride solution, and also solutions of other possible metallic contaminants, particularly nickel (using 10% nickel sulphate aqueous solution) and chrome (using 2% chromium sulphate solution). The establishment of such a state of sensitivity is determined by several factors, the most important of which is previous contact with the sensitizing substance. Either the wearing of the gold bracelets for several years or the wedding ring for three months would be a sufficient period of time for sensitization to be established. Other factors which play a part in the causation of sensitization dermatitis are alteration in hormone balance and emotional tension, both of these being present in the first few months of marriage and the pregnancy.

The sensitization established is usually very specific and there is not necessarily any association between certain detergents and 'dettol' and any other possible sensitizers.

In reply to the specific questions:—

(1) The state of sensitization once established will persist for a long time (perhaps throughout life).

(2) The most important therapeutic measure is complete avoidance of the substance to which the patient is sensitive. Local hydrocortisone will help to suppress the dermatitis.

(3) Desensitization to this type of allergen is not at present possible.

(4) There is no therapy (see 2).

(5) If the gold is definitely found to be the causative allergen, it will be necessary to change to an alternative precious metal. If nickel is the culprit, protection of the skin from all nickel (e.g. suspender buckles, clips) is imperative.

H. R. VICKERS, V.R.D., M.D., F.R.C.P.

Subluxation of the Shoulder

QUERY.—A young, powerful man of twenty-one, who is training to be a farmer in Africa, has a subluxating right shoulder posteriorly. He has had this as long as he can remember but it has

been worse recently. X-ray confirms that the head is riding up on the edge of the glenoid. The subluxation occurs when playing tennis and when lifting things with his arm raised. He can also subluxate his shoulder voluntarily. I would like to know the operation that should be recommended, the chance of success, and the prognosis if not operated on.

REPLY.—Posterior subluxation of the shoulder is an uncommon, but none the less definite, entity. No treatment other than surgical has a chance of success. There can be no sort of spontaneous improvement without surgery, and therefore this should be advised and accepted where the disability matters. The disability, however, is never very great, but this is one of the occasions when the patient is able to make use of surgery to improve his condition.

The operation of posterior bone block described by Victor Jones is theoretically first-class. It is impossible to estimate the recurrence rate because of the relative rarity of the condition.

RONALD FURLONG, M.B., F.R.C.S.

BCG Vaccination

QUERY.—My son is now 5 months old and I am wondering if he should receive BCG vaccination. There is no contact with tuberculosis in this case.

REPLY.—If you are anxious to take every precaution you may safely have your son vaccinated at any age, provided he is tuberculin-negative. Should you decide to have your son vaccinated now, you must make sure that he is retested at the age of thirteen and revaccinated then if necessary.

K. NEVILLE IRVINE, D.M.

Skin Protection in Basket Making

QUERY.—Some of the girls lacing baskets in a local factory using fresh timber have trouble with their fingers. They find that the skin on the finger-tips becomes quite white and if they continue at the work these begin to bleed. Apparently it is due, at least in part, to the acid pH of the sap. The present régime is to: (1) bind the finger-tips with adhesive tape (which they do not carry out conscientiously because it interferes with their dexterity in weaving the baskets, and also leaves black marks when removed in the evening), and (2) rub the finger-tips with methylated spirit.

I would be grateful for suggestions on alternative treatment as early as possible as production is at present seriously impaired.

REPLY.—I am not sure whether anything very useful can be suggested. I recall that Dr. Cruickshank of the Medical Research Council Unit for Research on the Experimental Pathology of the Skin had a similar case in girl salt packers. I imagine that both situations have in common a quite severe repeated friction of the finger-tips in circumstances where hardening by callus formation does not occur. I can only suggest alternative forms of physical protection which may well be no improvement on the methods already tried. There are on the market plastic fingerstalls which might be more convenient than adhesive strapping. One of the plaster manufacturers markets a special cruciform plaster for covering the finger-tips. This might be more convenient than what is at present used. (As for the difficulty with the black marks from the adhesive, these can usually be removed with a cloth moistened with trichlorethylene ['trilene']). Another form of protection that might be tried is one of the plastics in solution, such as 'portex plastic skin' or 'nobecutane' or collodion.

Different individuals might well prefer one of these rather than the others, but they are all attempts to the same end—the protection of the fingers from undue friction.

J. P. BULL, M.D.

'Chemical' Pregnancy Tests

QUERY (from a reader in Pakistan).—I have recently seen details of a chemical test for the early diagnosis of pregnancy. Are any such 'chemical' pregnancy tests of any value?

REPLY.—I very much doubt whether the suggested pregnancy test has any value at all. Up to the present time the only tests which have been shown to have any value in the early diagnosis of pregnancy are those based on the presence of chorionic gonadotrophin (HCG) in the urine. Since the amount of hormone protein in these early cases may be of the order of 0.2 mg. in a concentrated early morning urine specimen, and as in this concentration range there are many other mucoproteins present in the urine, it is doubtful whether any practicable chemical test will ever be sensitive or specific enough to form the basis of a reliable pregnancy test.

These considerations have led to the development of the various biological tests for HCG, Aschheim-Zondek, Fluhman ovarian hyperæmia, Xenopus toad and others which form the basis of modern practice.

The literature records a great deal of wasted effort spent on the investigation of so-called 'chemical' pregnancy tests.

PROFESSOR C. J. O. R. MORRIS, M.SC., PH.D.

Colouring Agents in Food

QUERY.—I have heard it said by colleagues that many colouring agents used in food, especially

in children's sweets, are carcinogenic. Is this true? If so, what is the risk to which children are exposed? Should doctors raise the matter with parents, who appear to be quite unaware of the existence of possible dangers of this kind?

REPLY.—The Ministry of Agriculture and Fisheries and Food issued an order towards the end of last year controlling the artificial colouring agents which could be used in food. All these colouring agents must eventually be tested for carcinogenic action and none which are considered to present a hazard from this point of view are allowed to be present in food.

PROFESSOR E. BOYLAND, D.SC.

Climate for Retirement

QUERY.—Have you any information regarding areas suitable for residence for an elderly couple, aged 67 and 71, suffering from catarrh of long standing, coupled with osteoarthritis of the spine and Ménière's syndrome? Both have spent several years in the tropics and many years ago both had severe malaria, now inactive. A climate which is mild all the year round within the British Isles is preferred and, being retired, I am not tied down to any particular area.

REPLY.—I doubt whether any place in the British Isles can be credited with a climate that is 'mild all the year round'. Resorts have seasonal advantages, all of which can hardly be expected throughout the year, and compromise is essential. Moreover one feels entitled to conclude from the nature of the inquiry that permanency is sought, a feature that increases the responsibility of recommendation.

Choice may be influenced by features other than climate, depending upon the inquirer's tastes and interests, for which reason I mention a number of places of widely differing character. Sidmouth, Falmouth and Cornwall generally, Ventnor and Bournemouth appeal to me as suitable. I think the first two should be visited as the strongest potential choice.

SIR ADOLPHE ABRAHAMS, O.B.E., M.D., F.R.C.P.

PRACTICAL NOTES

Griseofulvin

REPORTS are now beginning to appear of the results obtained with griseofulvin, the oral antibiotic for the treatment of superficial fungous infections. A. R. Birt and his colleagues (*Canadian Medical Association Journal*, August 1, 1959, **81**, 165) have used it in four cases of tinea capitis due to *M. canis*, two due to *M. audouini*, and one case of tinea corporis due to *T. mentagrophytes*—all of them children. The infections due to *M. audouini* responded very quickly. Those due to *M. canis* also responded favourably in the absence of follicular pustules. The drug, however, did not materially shorten the disease process when a follicular pustular reaction developed—as it did in two cases. Little effect was noted in the case of tinea corporis. No toxic effects were observed. N. M. Wrong and his colleagues (*ibid.*, p. 167) report on their results in 10 cases. These included seven patients with *T. rubrum*, in all of whom there was 'dramatic improvement' but 'in none could it be stated that a permanent cure was obtained'. Two patients with tinea capitis (one due to *M. audouini*, and one to *M. canis*) were 'apparently cured', but that due to *M. canis* was very slow in responding. The remaining patient, with tinea corporis, in whom no organism could be grown on culture, responded well. Toxic symptoms consisted of headache in two patients, and mild erythema of the nose in one. Anna Flint and her colleagues (*ibid.*, p. 173) report on its use in three cases of tinea capitis (*M. canis*) in children, four cases of tinea unguum (*T. rubrum* in three and *T. mentagrophytes* in one), and two cases of tinea pedis (*T. rubrum* in one, and *T. mentagrophytes* in one). All responded well, but the opinion is expressed that griseofulvin is 'particularly valuable in clearing up stubborn and resistant cases of tinea unguum . . . especially those infected with *T. rubrum*'.

Cold Foot and Myocardial Infarction

'"COLD FOOT" is a cardiovascular syndrome which is pathognomonic of silent myocardial infarction', according to N. Frank (*Journal of the American Medical Association*, July 4, 1959, **170**, 1147). He adds: 'When it occurs 4 to 21 days after operation in a patient without pre-existing heart disease or peripheral vascular disease, the patient probably has myocardial infarction'. Details are given of three such cases. The criteria laid down for the diagnosis of silent myocardial infarction in such cases are as follows. (1) Discovery of a cold foot. The contralateral foot should be warm or warmer than the affected extremity. (2) Absence of arterial pulsa-

tion in the foot and/or in other palpable arteries proximally. 'In other words, the dorsalis pedis pulsation should be absent'. (3) Plantar ischæmia of the foot on elevation. (4) Normal findings on clinical examination of the heart: i.e. sinus rhythm and no murmurs. 'If these simple criteria are satisfied', it is claimed, 'the diagnosis of silent myocardial infarction will almost invariably be correct'.

The Size and Number of Gall-stones

THE size and number of gall-stones found in patients submitted to cholecystectomy at the Mayo Clinic has been investigated by S. W. Carveth and his colleagues (*Proceedings of the Staff Meetings of the Mayo Clinic*, July 22, 1959, **34**, 371). A single stone was found in 119 (24.6%) of the 484 cases of acute cholecystitis and in 77 (18.5%) of the 416 cases of chronic cholecystitis. This difference of 6.1% is statistically significant. These solitary stones were 3 cm. or larger in 10.4% of the acute cholecystitis cases and in 2.4% of the chronic cholecystitis cases. The largest stone in the series measured 7 x 4.5 x 4.5 cm., and was removed from a 57-year-old man with acute cholecystitis. Multiple stones were found in 365 (75.4%) of the acute cholecystitis cases and in 339 (81.5%) of the chronic cholecystitis cases. The largest of the multiple stones (3 cm. or more in diameter) were present in 7% of the acute cases and 2.2% of the chronic cases. Stones, whether single or multiple, that ranged from 1.1 to 2.9 cm. in diameter were found with equal frequency in acute and chronic cases. On the other hand, multiple stones that varied from the class of 'sandy material' to 1 cm. in diameter were found slightly more often in cases of chronic cholecystitis.

Sensitivity of 'Albustix'

A COMPARISON of 'albustix', the colorimetric method of testing for proteinuria, and Heller's test has been made by K. Aukland and T. Lygren (*Scandinavian Journal of Clinical and Laboratory Investigation*, 1959, **11**, 172), based on the findings in 208 hospital patients and 271 'presumably healthy individuals serving in the armed forces'. They found that out of 105 Heller-positive urines, 17 gave a trace or negative reaction with 'albustix', and that out of 374 Heller-negative urines 82 (22%) gave an 'albustix' trace reaction. Quantitative estimations of the urinary protein were made in 226 cases. Of 64 urines which contained 0 to 5 mg. per 100 ml. of protein, 15 (23%) gave an 'albustix' trace reaction, but the bulk of the urines giving an 'albustix' trace reaction contained more than 5 mg. per 100 ml. of protein. An analysis of the results indicated that if all 'albustix' trace reactions are taken into account, a considerable number of physiological proteinurias will be included. Conversely, if trace reactions are considered as negative, the sensitivity of 'albustix' is somewhat less than that of Heller's test. It is considered that a sensitivity comparable to that of Heller's test will probably be achieved if colour changes corresponding to 30 mg. per 100 ml. on the 'albustix' chart and slightly greener are taken as positive reactions, whilst slighter colour changes are reported as negative. So far as quantitative assessments are concerned, it is considered that '"albustix" gives a fair clue as to whether urine contains small or large quantities of protein'.

Smoking and Gastrectomy

'IT had long been our conviction that continued smoking in the patient who had undergone gastrectomy was a significant factor in nutritional difficulties and the failure to gain weight following operation', according to W. F. Mitty, Jr., and his colleagues (*Annals of Surgery*, July 1959, **150**, 76). An investigation which they have carried out has failed to provide any statistical evidence to support this view, except in so far as 'late major complications' are concerned. The investigation consisted of a follow-up of 171 patients who had had a subtotal gastrectomy for gastro-duodenal ulceration. The minimum duration of the follow-up was two years. Of the 115 patients who were smokers, 59 (53%) lost weight postoperatively, compared with 27 (48.2%) of the 56 non-smokers. Of the 33 patients still complaining of indigestion, 21 were smokers and 12 were non-smokers. The 'dumping syndrome' was present in 15 (13.04%) of the 115 smokers and eight (14.2%) of the 56 non-smokers. Only eight of the patients had 'major late complications' (e.g. hæmorrhage, marginal ulcer, persistent vomiting) and they were all smokers. In the case of weight loss and gain, a comparison was made of those patients who both drank and smoked and those who neither drank nor smoked, and this failed to show any difference in the two groups.

Oleandomycin and Diphtheria Carriers

ENCOURAGING results are reported by A. Terragna and S. Scarabicchi (*Minerva Medica*, July 11, 1959, **50**, 2279) in the treatment of diphtheria carriers with oleandomycin, alone or combined with antidiphtheritic serum. Treatment was given for four to eight days to 55

healthy carriers aged 3 months to 32 years; in 34 the localization was pharyngeal and in 21 nasal. Bacteriological tests, performed every two or three days, were negative in all 55 carriers within 2 to 8 days. Oleandomycin was well tolerated, and there were no side-effects.

Wrist-strap Neuritis

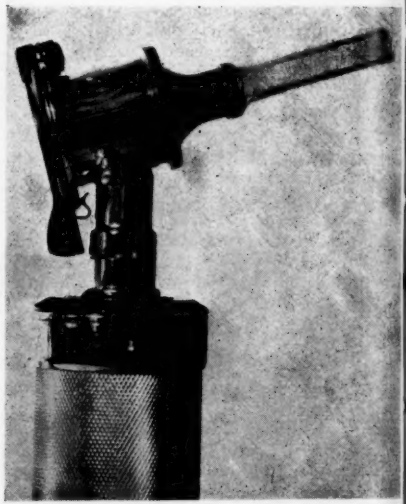
A CASE of progressive unilateral neuritis of the thumb and index finger, due to nerve compression by a wrist-watch strap, is reported by H. R. Bierman (*New England Journal of Medicine*, July 30, 1959, **261**, 237). The patient was a 34-year-old housewife, complaining of persistent numbness of the left thumb and index finger. On examination, there was hyperæsthesia of the entire thumb and thenar surface, and the lateral and volar aspect of the index finger were hyperæsthetic to the wrist. There was also wasting of the thenar eminence. Although there was no limitation of movement, there was weakness of thumb-to-finger adduction. The patient had thin forearms and wrists, and when she removed her wrist-watch from the left wrist there was seen to be a deep impression of the skin. Her history was that just before the numbness developed she bought a new strap for her watch. She admitted that it was a tight fit, but had thought that it would stretch. 'Unfortunately, the strap was constructed of narrow, thick, cured leather and failed to stretch as anticipated'. The other relevant point in her history was that she wore her watch continuously—night and day. In reporting this case the author comments: 'Perhaps a compression neuritis such as that described may occur more frequently than is realized'.

Finger-tip Hyperæsthesia

A NEW occupational disease of hairdressing is described by W. B. Shelley and D. M. Pillsbury (*Journal of the American Medical Association*, August 8, 1959, **170**, 1779). This is a persistent, punctate hyperæsthesia of the finger-tips, due to tiny particles of silica which become embedded in the epidermis and impinge on the sensory nerve-endings. The source of the silica is a new 'silicon hair curler'. This is covered with a fine granular material, presumably sand glued to a cardboard roller. In the course of use, the curler loses its rough surface and, once smooth, has to be discarded. The case recorded in this report was a 40-year-old hairdresser who had been handling as many as 450 of these a day, six days a week, for nearly three months. Superficial skin biopsies revealed the presence of many particles of silica in the stratum corneum. The superficial location of the particles renders their removal relatively easy by means of superficial razor biopsy. The authors comment: 'The recent widespread use of silica or sand-coated hair-curlers suggests that such an invisible foreign-body hyperæsthesia may become common among beauticians unless efforts are taken to eliminate this new occupational hazard'.

An Infant Proctoscope

A SIMPLE, rapid and atraumatic method of proctoscopy in infants, using an auriscope, is described by D. W. Furnas (*A.M.A. Journal of*



Diseases of Children, June 1959, **97**, 868). All that is required is to slip an appropriate length (5 cm. for the lower rectum) of plastic or rubber tubing over the end of the nasal speculum. A piece cut from a large catheter or a plastic rectal tube serves well. If plastic tubing is used, it should be heated with hot water and stretched on to the speculum with a hæmostat. The cut edge can be smoothed with an open flame. With the use of surgical lubricant, the end of the tubing is inserted into the anal orifice, with the infant in the knee-chest position. The auriscope light is then switched on and, under direct vision, the instrument can be inverted to the hilt of the speculum. To gain the optimal field of vision, care must be taken to keep the tubing in a straight line. This modified proctoscopy has been found of particular value in locating and removing foreign bodies in the lower rectum and 'in identifying minor pathology in this area'.

REVIEWS OF BOOKS

Human Nutrition and Dietetics. By SIR STANLEY DAVIDSON, M.D., F.R.C.P., F.R.C.P.ED., A. P. MEIKLEJOHN, D.M., M.R.C.P., and R. PASSMORE, D.M. Edinburgh: E. & S. Livingstone Ltd., 1959. Pp. xii and 844. Illustrated. Price 84*s.*

NUTRITION and dietetics have always been uneasy bedfellows. Mainly because, with one or two notable exceptions, nutritionists have refused to look upon man as anything else than an experimental guinea-pig (or rat). To them diets have only been combinations of proteins, fats and carbohydrates, with a few vitamins and minerals added. If these five factors were in the right proportions, and taken with the correct amount of fluid, then all was well. Unfortunately for their 'backroom' plans, man as often as not refused to react as a well-trained experimental animal. The dietitian, on the other hand, had to add a modicum of common sense. In so doing he produced a diet that was palatable and did what it was intended to do—much to the scornful consternation of the nutritionist.

This new book from the Edinburgh Medical School goes far towards overcoming these incompatibilities. The combination of a physician, a nutritionist, and a physiologist is a happy one, and between them they have produced the best practical book on the subject which has appeared for many years. From the clinician's point of view it is still rather unbalanced in favour of theory as against practice, and those of us who were brought up on another famous textbook on the subject by an Edinburgh graduate will wish that there were a few more practical hints for the harassed clinician and dietitian. We must be thankful, however, that it is as well balanced as it is. Its great merit is that none of the three authors have bees in their bonnets—or if they have, they have kept their buzzings well under control.

As a guide to nutrition there is no better book for the clinician, and he will go far before he finds a more useful guide to dietetics.

The Degenerative Back and its Differential Diagnosis. By P. R. M. J. HANRAETS, M.D. Amsterdam: Elsevier Publishing Co.; London: D. Van Nostrand Co. Ltd., 1959. Pp. x and 690. Illustrated. Price £5 5*s.*

DR. HANRAETS, of the St. Ursula Clinic in The Netherlands, has been struck by the unsatisfactory nature of our knowledge of the true character of low back pain which nowadays hampers so many people in their daily lives. He points out that the neurological symptomatology is apparently less watertight than had been supposed and that the erratic results of surgical treatment, despite increasing technical perfection, continue to be puzzling. He believes that the symptoms of back trouble seldom result from a single pain-producing mechanism and that it is not enough to attack the most obvious disturbing factor; the secondary circumstances partly responsible for the condition of the patient should likewise receive attention. The hernia nuclei pulposi should by no means be considered the only cause and, indeed, the syndromes often thought to point to such a hernia are by no means pathognomonic for this affection. The constitution is an essential factor in the pathogenesis of spinal complaints. In his view, an endogenously labile structure of the personality which implies abnormal psychomotor behaviour, exhibited by abnormal motor activities, is capable of weakening what was congenitally and initially a normal back, leading to a pathological condition. It should be realized, before all, that every sufferer from back complaints needs some form of therapy, but that not every patient is curable.

This is a unique and most important study of the degenerative back and is most thought-provoking as well as intensely interesting. It will undoubtedly make some contribution towards finding the most effective treatment for the patient suffering from a pathological back. It is well produced and illustrated, though the coloured pictures are not of a high standard. The reviewer warmly recommends it, particularly to neurosurgeons and orthopædic surgeons.

Surgery of the Ear. By GEORGE E. SHAMBAUGH, JR., M.D. Philadelphia and London: W. B. Saunders Co., 1959. Pp. viii and 669. Figures 326. Price £7 12*s.* 6*d.*

THIS is an excellent book and it presents a complete and up-to-date, almost up-to-the-minute, account of the surgery of the ear. As the author points out, no branch of surgery has advanced more rapidly in recent decades than otology. It has been profoundly benefited by the introduction of sulphonamide and antibiotic therapy. It is of interest to note that, while the section on the surgery of infection of the ear occupies 174 pages, that on the surgery of deafness extends to 269. The book is profusely illustrated and the illustrations are clear and most helpful, particularly those of operations done under magnification. There is an excellent chapter on radiological examination of the temporal bone which is well and instructively

illustrated. The chapter on the mechanism of hearing is most interesting and a very good résumé of present-day knowledge. In dealing with carcinoma of the ear (of the external auditory meatus and middle ear) wide surgical excision by means of an extensive radical mastoid operation is advocated but, instead of following this with therapy by external radiation by cobalt beam or some other form of high-voltage therapy, as is the practice in this country, it is recommended that the interstitial application of radium needles be used. This is not the best treatment and certainly in this case treatment in this country is in advance of that in the United States.

The book is well written and well produced. It is pleasing to see the brief historical allusions and the photographs of the pioneers of otology which head the various sections. Altogether one may say that this is by far the best book on the surgery of the ear that has appeared for a long time and it is one that any otologist will find most practical, useful and instructive.

Elementary Medical Therapeutics. By G. F. WALKER, M.D., M.R.C.P., D.C.H., F.R.F.P.S. Bristol: John Wright & Sons Ltd., 1959. Pp. 64. Price 7*s.* 6*d.*

THIS slim pocket-book presents a brief and simple approach to elementary therapeutics; Dr. Walker's maxim that 'it is better to know a few drugs thoroughly than a large number vaguely' proves a useful finding principle. Drugs are grouped and described by their therapeutic action; the text is remarkably up to date and in this respect analeptics and hormones are particularly good sections. Anthelmintics are perhaps too briefly described and precautions in administering anticoagulants could well be expanded. This, however, does not detract from the value of this book for senior students and house officers and if they use it as regularly and frequently as expected, a better-quality stiff cover and index might well be considered for future editions.

Modern Trends in Pathology. Edited by DOUGLAS H. COLLINS, O.B.E., M.D., F.R.C.P. London: Butterworth & Co. (Publishers) Ltd., 1959. Pp. x and 346. Figures 135. Price 70*s.*

THIS volume is the work of sixteen eminent pathologists who have contributed fifteen chapters under the editorship of Professor Douglas H. Collins. Its international character is maintained by two contributors from the United States and one from Uganda. The subjects are mainly in the field of morbid anatomy although individual chapters have special interest for the serologist and biochemist. The selection of topics is appropriate to the title since it is not entirely a record of recently completed work as implied by such terms as 'recent advances', but a survey of certain fields in which important progress is being made: the growing-point of pathology. We are taken to the last point of accomplishment and then the outstanding deficiencies are indicated and unanswered questions clearly stated. Where all the chapters are of exceptional merit it is invidious to select any for special mention but those by Sir Roy Cameron on the injured cell, Murray Angevine on injury to connective tissue and A. C. P. Campbell on the malignant carcinoid syndrome serve to indicate the topicality of subjects and the authority of the contributors. The trend is defined with remarkable unanimity by all the authors. It is that morbid morphology is not enough. The pathologist must employ the methods and acquire the experimental outlook of the physiologist, the embryologist, the biochemist and the biophysicist if the manifold problems so clearly presented here are to be solved.

This book is not for fireside recreational reading but it constitutes a strenuous and intensely absorbing course of postgraduate study as well as a stimulant and fertilizer of research projects. It should be in every area laboratory and a second copy could well find a place in the hospital library where clinicians old and young will gain inspiration from it.

The Management of Emergencies in Thoracic Surgery. By JOHN BORRIE, M.B.E., CH.M., F.R.C.S., F.R.A.C.S. London: Staples Press, 1959. Pp. xi and 340. Illustrated. Price 84*s.*

ONE of the special merits of John Borrie's writings is that, being a practical man, he describes the details of surgical emergencies in the thorax clearly, briefly, and in such a way that the procedures are rational and easy to follow. Reading this book one feels that he has not only profited from the manifold experiences of other surgeons (there are well-selected bibliographies at the end of each chapter) but he has tried out every step he recommends. He writes from personal experience. The book starts with three chapters that cover the basic principles of thoracic surgery. It continues with descriptions of chest-wall injuries and their effects; pleural emergencies, pulmonary emergencies, œsophageal, mediastinal and diaphragmatic emergencies follow, and the book ends with a description of cardiac arrest, hæmopericardium and purulent pericarditis. There is a large number of x-ray reproductions and simple line

drawings; his style is crisp and the English good.

This book will be valuable to house surgeons—and especially to those whose knowledge of chest disease and operations is flimsy; as a reference work it will be useful to those who know the subject, but who wish to have a comprehensive description of each topic at their finger-tips; and to those who propose to sit for higher examinations it will save hours of search through papers and monographs. This book combines simple advice and scholarly argument.

The Plasma Proteins. By PAUL G. WEIL, M.D., PH.D. Philadelphia: J. B. Lippincott Co.; London: Pitman Medical Publishing Co. Ltd., 1959. Pp. xvi and 133. Price 28*s.*

Too much cannot be expected from a book of little over 100 pages on the plasma proteins. Nevertheless, within its limited compass this small volume covers an astonishing amount of ground and makes intelligent comment upon many of the clinical conditions associated with plasma protein abnormalities. The various methods of measuring or defining the physical characteristics of plasma proteins are dealt with in an early chapter. Thereafter there is mention of such syndromes as that of Hamman-Rich, amyloidosis, cryoglobulinæmia, auto-immunizing disease and many others in which protein metabolism plays a basic part. In one sense this book is no more than a vocabulary, but it is a vocabulary of one language which renders intelligible a wide variety of clinical states.

Medical Laboratory Investigations: Their Use and Interpretation. By IAN DAWSON, M.D., M.R.C.P., and WILLIAM GOLDIE, M.B., F.R.C.P. London: Butterworth & Co. (Publishers) Ltd., 1958. Pp. xv and 260. Figures 5. Price 35*s.*

THIS excellent book written by two well-qualified and experienced pathologists is designed to link clinical and laboratory medicine. It sets out clearly what can be done in the various laboratories to help in diagnosis; even more important, it gives a critical appraisal of the usefulness of the various tests commonly employed. As with all new books there are small points with which one cannot agree, but these are trivial in comparison with the wide scope of the book. Throughout, the material has been prepared with meticulous care and is so well up to date that the book is not likely to be superseded for many years.

This book, which has no exact counterpart, is a necessity. It should be available to every clinician and should occupy a convenient place in every hospital side-room. Equally well it should be in every laboratory so that the pathologist may know what his clinical colleagues are thinking.

Principles of Medicine for Nurses. By DAVID WEITZMAN, M.D., M.R.C.P. London: Faber & Faber, 1959. Pp. 237. Illustrated. Price 21*s.*

THIS is a welcome addition to the textbooks of medicine at present available to the student nurse, and to the trained nurse as well. The General Nursing Council syllabus is fully covered, and the subject-matter presented in a clear, concise and yet delightfully readable manner. Discussions of the outline pathology and symptoms resulting from disease of the various systems has been simplified by a brief description of the relevant anatomy and physiology; the use of normal x-ray film reproductions to contrast with the abnormal is a most welcome feature. In general, treatment is well described but in future editions the section on diabetes could advantageously include a more detailed account of diabetic coma and ketosis, and some brief mention be made of radioactive isotope therapy. The excellent quality of the illustrations and the useful 'glossary of technical terms' help to complete a comprehensive textbook that should prove very popular.

Social Work in Tuberculosis. By MARGARET COLTART, M.A., A.M.I.A., HELEN RAINE, B.A., and ELIZABETH HARRISON. London: The Chest and Heart Association, 1959. Pp. vi and 137. Price 12*s.* 6*d.*

THIS small book is designed for the use of students in social work and others interested in that particular field. It should prove of great assistance to workers in less well-developed countries where tuberculosis control programmes are still in embryo and where the problems which the authors have met and overcome so successfully have yet to be encountered. The diversity and fascination of these problems are excellently depicted in the various case histories with which the text is liberally documented and which add greatly to the practical value of the book, as does also the section dealing with the complex subject of the help available from statutory and voluntary sources. Whilst the book deals specifically with the social aspects of tuberculosis, there is much in it which could be applied equally well to the problems posed by any chronic disease when tackled with the enthusiasm and sense of dedication shown by the authors.

NEW EDITIONS

A Textbook of Medicine, edited by Russell L. Cecil, M.D., SC.D., and Robert F. Loeb, M.D., SC.D., in its tenth edition (W. B. Saunders Co., £5 15*s.* 6*d.*) maintains the high standards of its predecessors. It has undergone careful revision, and numerous new sections have been included, covering subjects such as adenoviral infections, Echo viral infections, amino-aciduria, and steroid physiology and metabolism. In the reviewer's opinion this is the best textbook of medicine in the English language at the present moment. It is comprehensive, balanced and never befogs the issue with a mass of irrelevant detail. Throughout, the contributors concentrate on those practical aspects which are essential to the practising clinician.

British Obstetric Practice, edited by Sir Eardley Holland, M.D., F.R.C.P., F.R.C.S., F.R.C.O.G. (William Heinemann Medical Books Ltd., £7 7*s.*), in its second edition, is the second volume of 'British Obstetric and Gynæcological Practice', and contains two excellent new chapters: on the function of the placenta and on birth-adaptation from intra-uterine to extra-uterine life. In a book of this size, with 42 contributors, there is certain to be some overlapping of subjects and also some contradictions, and this was a criticism of the previous edition. Efforts have been made by the editor to overcome these criticisms. The book consists essentially of a series of signed monographs written by authorities in each particular field and some of these contain unorthodox views. It is imperative that each author should fully cover his subject even if as a result there is some overlapping. The name does suggest that there is some unified British practice, which to those who have memories of examinations from both sides of the table will know to be far from the true position.

The book is intended for those with some specialized knowledge of the subject. It is therefore annoying to find some chapters containing material which might be from an introductory book on obstetrics. Reading is made more difficult in many instances by too frequent references, sometimes irrelevant or out of date. These are minor criticisms, and the book can be thoroughly recommended as an excellent reference book which will certainly help to enhance the reputation of British obstetrics.

Recent Advances in Cardiology, by Terence East, D.M., F.R.C.P., and Curtis Bain, M.C., D.M., F.R.C.P., in its fifth edition (J. & A. Churchill Ltd., 45*s.*) has been completely rewritten. It is a sign of the times that, although somewhat smaller than the previous edition published just over ten years ago, the price is almost twice as much. It is still good value for money, however. The emphasis throughout is on the practical aspects of the subject which will be of interest to the clinician. This is not a collection of advances for advance's sake. It is a careful assessment of advances by two experienced cardiologists. Conservatism may be the keynote of the book, but that is no bad thing in these days of uncritical acceptance of what is new.

Behandlung innerer Krankheiten, by Professor Dr. Ferdinand Hoff, in its eighth edition (Stuttgart: Georg Thieme Verlag, DM 59.50), has been increased by about 100 pages, due mainly to new sections on harmful effects caused by modern therapeutics (e.g. allergic reactions to penicillin and toxic effects caused by 'fresh cell therapy') and treatment of conditions caused by poisons or intoxications. The book deals with the infectious cardiovascular diseases; diseases of the respiratory tract and of the blood; malignant tumours; disturbance of internal secretion; metabolic diseases; diseases of the digestive tract, of the urogenital system and muscle and bone diseases, concluding with a chapter on nervous diseases. As in previous editions, an account is given of drugs, the quantities in which they are normally supplied, and the prices. The critical appraisal of the most recent treatment of malignant blood diseases and of the value of cortisone treatment of infectious diseases deserves to be mentioned. These critical views, in particular that on the 'fresh cell therapy' expressed by a leading university clinic in Germany, are of interest to both the practitioner and the specialist in this country.

Postural Drainage and Respiratory Control, by E. Winifred Thacker, M.C.S.P. (Lloyd-Luke (Medical Books) Ltd., 10*s.* 6*d.*).—In the second edition of this successful handbook the title has been expanded in accordance with the wider range of chest management now covered. It contains more technical information than the term postural drainage by itself would imply. This change has added value to a book which, in other respects, has required little alteration. It remains an exceedingly useful, well-illustrated guide to an important subject.

The contents of the November issue, which will contain a symposium on 'Virus Diseases,' will be found on page A 158 at the end of the advertisement section.

Notes and Preparations see page 545.
Notes from the Continent see page 549.
Fifty Years Ago see page 551.
Motoring Notes see page A 105.
Travel Notes see page A 109.
Bridge Notes see page A 113.
Approved Names see page A 115.

NOTES AND PREPARATIONS

NEW PREPARATIONS

'BIMEZ' tablets each contain 0.375 g. of sulphadimidine B.P., and 0.125 g. of sulphadimethoxypyrimidine and are intended for the treatment and prophylaxis of bacterial infections which are sensitive to the sulphonamides. A single daily dose is said to provide 'persistent sulphonamide blood levels'. Issued in containers of 12, 50 and 500 tablets. Also available as 'bimez suspension' (one 3.5-ml. teaspoonful is equivalent to one tablet) which is said to be especially suitable for children and the elderly. Issued in bottles of 30 ml. (Imperial Chemical Industries Ltd. (Pharmaceuticals Division), Fulshaw Hall, Wilmslow, Cheshire.)

'DISAMIDE' tablets each contain 100 mg. of 5-chloro-2-4-disulphamyltoluene, which is a 'potent' oral diuretic. It is said to be well-tolerated, even for long periods of treatment, and side-effects of toxic origin are said to be very rare. Available in bottles of 25, 100 and 500 scored tablets. (The British Drug Houses Ltd., Graham Street, London, N.1.)

'ECOMYTRIN' ointment contains 0.5% amphomycin (as the calcium salt) and 0.33% neomycin B base (as the hydrochloride) and is intended for topical application in 'all skin disorders of bacterial origin'. The 'special vanishing cream base is an oil-in-water emulsion with the drugs in the continuous phase, ensuring intimate contact with the skin and maximum antibacterial effect'. Bacterial strains resistant to penicillin, chlortetracycline and oxytetracycline are said to be sensitive to amphomycin, which has the added advantage that it is not used systemically. Available in tubes of 15 g. (William R. Warner & Co., Ltd., Eastleigh, Hampshire.)

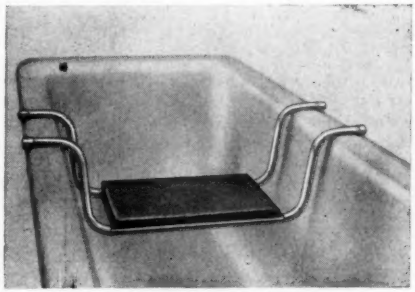
'SUSTAC' (sustained action) tablets contain glyceryl trinitrate and are indicated in the treatment of angina pectoris. They are specially processed to allow uniform release of the drug over periods of up to ten or twelve hours after ingestion, and one tablet night and morning therefore affords 'round the clock protection against anginal attack'. Available as tablets of 1/25 and 1/10 grain (2.4 and 6 mg.) in bottles of 30. (Pharmax Ltd., Western House, Gravel Hill, Bexleyheath, Kent.)

PHARMACEUTICAL NOTE

BOOTS PURE DRUG CO. LTD. announce that their hydroflumethiazide preparation, 'hydrenox', is now available in a lower strength of tablet (25 mg.) 'to facilitate the treatment of several conditions (particularly hypertension and premenstrual œdema) where lower doses are effective'. These tablets will be known as 'hydrenox-M' and will be coloured white instead of yellow. Issued in containers of 100 and 500. (Station Street, Nottingham.)

NEW APPARATUS

'ECONOMIC' bath safety seat is designed for 'persons handicapped by age or infirmity, and who find it difficult or impossible to sit in a bath',



and will carry a weight of 40 stones (250 kg.). The standard size will fit baths with an inside width of from 21 to 23 inches, measured at a height of two inches below the top of the bath, and the parts that come in contact with the bath are covered with protective plastic. (Charles Winn & Co. Ltd., Granville Street, Birmingham, 1.)

'RESTALL' is the name of a new 'featherweight' bedrest which is moulded in resilient plastic foam. It provides firm support for invalids or elderly people confined to bed, while allowing freedom of movement for light activities. It is provided with side pockets to hold spectacles, handkerchiefs and other oddments, and loose covers with special 'popper' fasteners for easy laundering are also available. (Slumberland Ltd., Redfern Road, Tyseley, Birmingham.)

ROYAL SOCIETY OF MEDICINE

THE next meeting of the Section of General Practice will be held at 8.15 p.m. on October 21, when the valedictory address on 'Rheumatology in General Practice' will be given by Dr. G. J. V. Crosby, C.B.E.

The November meeting of the Section will be

held at 8.15 p.m. on November 18, when the subject for discussion will be 'The Ageing Mind'. The opening speakers will be Drs. Annis Gillie, T. N. Rudd, and E. Beresford Davies.

EXHIBITIONS

An exhibition of *Medical Photography* will be presented by the Medical Group of the Royal Photographic Society at the Society's House, 16 Princes Gate, London, S.W.7, from November 12 to 19, 1959, inclusive.

The *London Medical Exhibition* will be held in the New Hall of the Royal Horticultural Society, London, S.W.1, from November 16 to 20 inclusive. It will be officially opened by Sir Daniel Davies, K.C.V.O., M.D., F.R.C.P.

The third *Doctors' Hobbies Exhibition* organized by Benger Laboratories Ltd. will be held in the Great Hall, B.M.A. House, Tavistock Square, London, W.C.1, from November 16 to 20, 1959, inclusive.

The 44th *London Nursing Exhibition* organized by the *Nursing Mirror* will be held at the Seymour Hall, Seymour Place, London, W.1, from October 12 to 16 inclusive. Members of the medical profession and other professional visitors can obtain free tickets of admission from the Organizer, London Nursing Exhibition, Dorset House, Stamford Street, London, S.E.1, or by producing their professional card at the entrance.

DESIGN OF DOCTORS' SURGERIES

The autumn programme of the Design Centre, 18 Haymarket, London, S.W.1, includes a furnishing scheme for a doctor's waiting-room and surgery, which is 'practical, but more cheerful than usual'. This will be on display from November 2 to 28.

JAMES MACKENZIE LECTURE

The sixth James Mackenzie Lecture of the College of General Practitioners will be given by Dr. J. A. Llewellyn Vaughan-Jones at 11.30 a.m. on November 21, 1959, in the Great Hall, B.M.A. House, Tavistock Square, London, W.C.1. The title of the lecture will be 'The General Practitioner and Industrial Health'.

THE HARBEN LECTURES

The Harben Lecturer for 1959 is Sir Francis Walshe, whose subject will be 'The Evolution of Ideas in Neurology During the Past Century, and the Future of Neurological Medicine'. The lectures will be given at 5 p.m. on December 8, 9 and 10, 1959, in the Lecture Hall of the Royal Institute of Public Health and Hygiene, 28 Portland Place, London, W.1.

B.M.A. SCHOLARSHIPS

The Council of the British Medical Association invite applications for the following research scholarships:—An *Ernest Hart Memorial Scholarship* (£300), a *Walter Dixon Scholarship* (£300) and four Ordinary Research Scholarships (£200 each). The scholarships will be given to candidates recommended by the Science Committee of the Association as qualified to undertake research in any subject (including State Medicine) relating to the causation, prevention or treatment of disease. The *Insole Scholarship* (£250) will be awarded for research into the causes and cure of venereal disease. Applications, including renewals, must be made not later than March 1, 1960. Full details may be obtained from the Secretary, British Medical Association, B.M.A. House, Tavistock Square, London, W.C.1

THE CIBA FOUNDATION

The decennial report of the Ciba Foundation, covering the first ten years of its existence (1949-1959) is one of continued progress and ever-increasing service to its declared aim: 'the promotion of international cooperation in medical and chemical research'. Its symposia are internationally famous and are now looked upon as a unique clearing-house for the dissemination of the latest information on the subjects with which they deal. Equally famous is the hospitality which the Foundation dispenses to visitors from abroad. There will be many a scientist in many a country who, in his own language, will subscribe to the old Scottish wish: 'Lang may your lum reek'.

THE KING'S FUND

The capital resources of the King Edward's Hospital Fund for London, according to the recently published annual report for 1958, now total some £8 million, with an annual income of around £430,000. In 1958, the income amounted to £430,127, £227,798 of which came from legacies. The expenditure was £427,534. This included £254,300 as grants to hospitals, and £25,000 to convalescent homes. Of the grants made to hospitals, just under £160,000 went to mental hospitals. The independent hospitals, which are outside the National Health Service and therefore entirely dependent upon voluntary support, have not been forgotten. The largest grant in this category was a further £5000 to the French Hospital, towards a scheme of rehabilitation costing in all £40,000.

GENERAL PRACTICE IN NORTHERN IRELAND

'THE problem of inflation of doctors' lists continued to cause concern', according to the annual report for 1958-59 of the Northern Ireland General Health Services Board. 'Despite all the Board's efforts', the number of persons registered on doctors' lists in 1958-59 was 0.6% higher than the latest available estimate of the civilian population. The number of doctors in practice as principals fell from 737 to 731. The total number of assistants was 114. Seven refresher courses for general practitioners were held during the year, attended by 94 doctors. In discussing the doctor-patient relationship it is stated that 'a comparatively small number of inconsiderate or thoughtless patients create much difficulty for doctors by unreasonable and unnecessary demands, sometimes under threat of transfer to another doctor'.

AMERICAN PHARMACEUTICAL RESEARCH

IN an article in the *New York Journal of Commerce*, quoted in the *Pharmaceutical Journal*, the sales manager of Lederle Laboratories Division, American Cyanamid Co., forecasts that in 1959 the United States pharmaceutical industry's expenditure on research will reach 190 million dollars. This will represent a 50% increase over 1957. This is an indication of the industry's faith in its future, and it is forecast that the present 1.8 billion dollars United States market at the manufacturers' level will rise to 5 billion dollars within the next ten years. This will be achieved in three ways; by the discovery and development of new drugs effective against diseases not controlled by existing drugs; by improving and finding new uses for existing drugs; and by continuing foreign expansion.

RECIPROCITY WITH DENMARK

A CONVENTION on Social Security between the United Kingdom and Denmark has been signed, which covers all the benefits provided by the schemes of National Insurance, Industrial Injuries Insurance and Family Allowances in this country and the corresponding benefits in Denmark. People insured in both countries will be able to add together contributions paid in the two countries in order to determine the right to receive benefit. In addition, medical treatment will be available under the Danish scheme of sickness insurances in Denmark for all British nationals in Denmark and their dependants who are in urgent need of medical treatment whether they are working or on holiday there. The Convention will come into operation when it has been ratified; this date will be announced in due course.

A HOME FOR DEAF CHILDREN

THE National Deaf Children's Society is now running a Home where children can go for holidays, for convalescence or in case of emergency. The Home, situated in 3½ acres of lawns, orchards, kitchen garden and paddock, is Woodfield, the country house at Burgess Hill, Sussex, of Major and Mrs. Whitelock, who have cared for children there for 20 years and now have a financial arrangement with the National Deaf Children's Society for the care of deaf children. The Home will take girls up to 11 years and boys up to 10 years of age.

BROWN MILK BOTTLES

BROWN milk bottles are now being used in Denmark in order to reduce the loss of vitamin C which milk undergoes when exposed to sunlight in clear bottles. It is estimated that the loss of vitamin C in milk exposed to sunlight in clear bottles is 79%, compared with only 1.3% in brown bottles.

PUBLICATIONS

A Pocket Book of Proprietary Drugs, compiled by Alistair G. Cruikshank, F.R.C.P.ED., and Cornelius Stewart, L.R.C.P. & S., M.P.S., is a list of some fifteen hundred proprietary preparations, arranged alphabetically and giving the composition, indications, packs and dosage. It will prove of the greatest value to the general practitioner: so much so, that the authors and publishers are almost bound to find themselves committed to publishing a new and revised edition annually. This being so, the value of future editions would be considerably enhanced if they contained an alphabetical list of approved and official names giving cross-references to the proprietary equivalents. (E. & S. Livingstone, Ltd., price 10*s.* 6*d.* An interleaved copy is also available, price 14*s.*)

Principles and Practice in the Management of Surgical Patients, by A. Venugopal Mudaliar, M.S., has been written with a limited but very important aim: to help those men—the young surgeons who have obtained or are about to obtain higher qualifications—on whom the success of the surgery and the reputation of their hospitals will in the future depend. He has succeeded admirably. He has brought the book within tolerable confines by omitting details of those major operations at which his readers will help but which they will not as yet perform, but giving all those details of preoperative investigation and preparation and postoperative care on which their success as juniors and their future ability as mature surgeons will depend. The illustrations are excellent. This book deserves and should attain

a large sale in India among those who are helping to build the reputation of that great country. (G.S. Press, Madras, price 30*s*.)

Common Ailments in Toddlers, by R. S. Illingworth, M.D., F.R.C.P., D.P.H., D.C.H., is a useful addition to the *Family Doctor* series of booklets, and covers 'all the common ailments and problems that beset toddlers and bother their parents'. (British Medical Association, Tavistock Square, London, W.C.1, price 1*s*.)

That the Patient May Know, by Harry F. Dowling, M.D., Sc.D., and Tom Jones, B.F.A., is described by the authors as 'an atlas for use by the physician in explaining to the patient'. For those practitioners who wish to give their patients a detailed account of the why and wherefore of their illness it will subserve a useful function. Its major value in this country, however, will be for those who lecture on health matters to the public. (W. B. Saunders Co., price 52*s*. 6*d*.)

The Story of Medicine, by Kenneth Walker, M.B., F.R.C.S.—This light edition is an ideal bedtime book for doctors; it tells old tales they've heard in part before, it is fluent so that one can almost hear the bedtime voice, it is gently humorous even in depicting gruesome scenes, e.g. Ambroise Paré's wartime surgery, Cheselden's lithotomy in 54 seconds, Larrey's 200 amputations at the Battle of Borodino, Hare and Burke's guest-house for vagrants, all of which seem to make the bed more snug. It takes us back to times when men were groping with many problems of which we now know the solutions, giving a quietly superior feeling; it makes us feel we have been in these places and circumstances before and have a murky nostalgia for them, that we witnessed the barbaric deeds or grisly happenings recounted, catching the contagion of our forbears' terror from ignorance, wonder at the dawns of knowledge, and triumph at a step or two ahead. In short it makes us regress to earlier times—which is the very essence of sleep. (Arrow Books Ltd., price 5*s*.)

Notes of a Soviet Doctor, by G. S. Pondoev, translated by Basil Haigh, M.B., B.CHIR., is an exposition of medical ethics and conduct in the U.S.S.R., by a Russian doctor who has practised under both the Tsarist and Soviet régimes. Platitudinous and pedantic though it may be, it throws an interesting light on the valiant attempts that our opposite numbers on the other side of the Iron Curtain are making to make the best of both worlds—that of Hippocrates and that of Karl Marx. (Chapman & Hall, price 40*s*.)

Notification of Communicable Diseases is reprinted from the WHO 'International Digest of Health Legislation', and covers the legislation of about fifty countries. It includes a useful section listing notifiable diseases alphabetically according to country. (H.M. Stationery Office, price 3*s*. 6*d*.)

The Ecology of Human Disease, by Jacques M. May, M.D., is the first volume of a three-volume work dealing with the relationship between disease and the geographical environment in which it occurs. Among the diseases dealt with in this volume are tuberculosis, leprosy, poliomyelitis and measles. It is an interesting book which will prove particularly valuable as a work of reference (MD Publications Inc., price $7.50.)

Preparation for Retirement is a brief report on the work of a special study group set up by the National Old People's Welfare Council in 1955. (National Council of Social Service, 26 Bedford Square, London, W.C.1, price 1*s*. 6*d*.)

The Story of Evans Medical is a beautifully produced book which has been published to commemorate the 150th anniversary of the foundation of Evans Medical Supplies Ltd. It includes an interesting outline of the main events in the company's history, from its foundation by John Evans in 1809 to the occupation of the research laboratories at Speke in January 1959.

OFFICIAL PUBLICATION

Standards of Normal Weight in Infancy (Reports on Public Health and Medical Subjects No. 99) is the report of a committee set up as the result of a request from the British Pædiatric Association to the Ministry of Health that up-to-date figures should be collected on the growth of young children. Hitherto the standards used in this country have been based on figures collected at the beginning of the century or derived from American sources. The report is based upon a survey of 17,308 children and shows that the average birth weight of boys is 7.3 pounds and that of girls 7.21 pounds. The gain in weight from birth to 3 years is largely, but not entirely, independent of birth weight. In the first few months smaller babies grow more rapidly than larger babies, but later the trends are recessed. Gain in weight after birth is greater for bottle-fed babies than breast-fed babies, and for children of the professional and managerial classes than of the unskilled classes. (H.M. Stationery Office, price 2*s*. 6*d*.)

CORRIGENDUM.—Professor P. C. Koller has asked us to state that on page 699 of his article in our June issue the word 'Hindus' in the penultimate line should read 'Moslems'.

NOTES FROM THE CONTINENT

A European Newsletter

GERMANY

Congenital deformities and nuclear explosions.—According to E. V. Schubert, there is no evidence of any correlation between the explosion of atomic bombs and the increase in such deformities in Germany between 1950 and 1957. Such assertions, he contends, are based upon inexact statistical evidence. As he further points out, the degree of radiation after such explosions is much smaller than that which has been shown by laboratory experiments to be necessary to cause such deformities.

R. Hohlbein has analysed the incidence of congenital deformities which occurred in Dresden between 1921 and 1958. Among 129,382 births there were 748 congenitally abnormal children: an incidence of 0.58%. In 1946-1950 the number of deformities was significantly increased. This he attributes, in part at least, to the psychic stress of the war and the post-war years. Like all investigators in this field, he stresses the importance of avoiding unnecessary x-ray examinations during pregnancy.

Hyaluronidase and parturition.—H. Belz recommends the use of hyaluronidase as a means of facilitating childbirth. This it does, it is claimed, by softening the connective tissues. He finds it particularly useful in the primigravida with a rigid perineum, and injects 150 units of hyaluronidase into the perineum about ten to fifteen minutes before the passage of the head through the vagina. By this method the number of episiotomies is said to be reduced.

Plasma substitutes and blood grouping.—Attention is drawn by H. J. Pettenkofer to the error in blood grouping that may arise from the use of colloidal plasma substitutes. Like all colloids, plasma substitutes increase the tendency to agglutination in red blood cells, and this may lead to serious errors. It is therefore recommended that blood should be withdrawn for grouping before the administration of plasma substitutes.

Thermo-electric temperature recordings. — A thermo-electric method of recording the temperature by means of a light-galvanometer is described by P. Biesalski. He has found it particularly useful in infants, in whom it is so often difficult to obtain an accurate record of the temperature. The measurements are taken on the nasal mucous membrane by means of a small delicate terminal. The temperature reading, which can be made in two to ten seconds, is recorded by a beam of light falling on a specially graduated scale. One of the special uses of this method is in the diagnosis of obscure infections of the auditory tract. It is claimed that in such cases thermo-electric temperature readings are higher in the affected ear than in the normal one.

Refugee doctors.—The number of doctors who fled from the Soviet zone to Western Germany rose rapidly last year. The number who fled in 1958 (901) was practically as great as in the whole of the preceding four years. The figures for the last seven years (i.e. from 1952 to 1958) are: 187, 328, 145, 202, 290, 298, and 901.

Meals à la carte.—In two large Munich hospitals patients are now provided with meals 'à la carte'. As in a hotel, patients are allowed to choose from a menu, the only restrictions being those imposed by the condition for which the patient is undergoing treatment. The patients, needless to say, are delighted with the scheme, and it has proved so successful that the system is to be introduced in all the hospitals in Munich.

Respiratory disease and industry.—In the Federal Republic 26 million working days are lost every year on account of respiratory disease. This compares with an annual loss of 5 million days from tuberculosis. The difference is all the more striking in view of the much longer duration of incapacity for work in the case of tuberculosis, compared with most non-tuberculous respiratory infections. It is estimated that the loss to industry arising out of respiratory illness is in the region of 400 million DM annually.

'*Struwwelpeter*'.—Whether shock-headed Peter is still a popular figure in the nursery may be problematical in these days when child psychiatrists exercise so much control over the rising generation, but the older generation will be interested to know that June 15 was the 150th anniversary of the birth of the author of this nursery classic—Heinrich Hoffmann, who was a Frankfurt doctor.

ITALY

Yttrium^{90} in the treatment of acromegaly.—Satisfactory results are reported by A. M. Dogliotti and his colleagues from irradiation of the pituitary gland by yttrium^{90} in the treatment of five cases of acromegaly. Making full allowance for the relatively small number of cases, and the shortness of the follow-up period, they summarize the effects of such treatment as follows. That there is inhibition of excessive somatotrophic activity of the hypophysis is indicated by the disappearance or diminution of alterations in glucose and calcium metabolism. There is no evidence of any inhibitory effect on the thyroid, suprarenals, or gonads. Immediately following irradiation there may be stimulation of the other activities of the diencephalon as manifested by diabetes insipidus and increased disturbance of glucose metabolism. This, however, is not a contraindication to the use of yttrium^{90}, as these disturbances are only of temporary duration. The approach used by the authors is the intranasal, trans-sphenoidal route, implanting two needles—one on either side of the antero-posterior axis.

Neurogenic mediastinal tumours.—In a series of 47 tumours of the mediastinum, P. Bucalossi and his colleagues found 11 (23.4%) of neurogenic origin. These included three sympathicoblastomas, two ganglioneuromas, four schwannomas, and two malignant schwannomas. These all originated in the costo-vertebral sulcus and invaded the posterior mediastinum—usually on the right side and in the upper part of the mediastinum. The presenting symptom was pain, corresponding to the side of the chest involved: in two cases the pain had been present for six and seven years, respectively, when the patient was first seen. In three cases, in which the tumour had spread into the anterior mediastinum, there was venous congestion of the upper limb on the affected side, as well as shortness of breath. Surgical treatment was carried out in nine cases. In a follow-up period, varying from ten years to eight months, three deaths had occurred: two of the patients with sympathicoblastomas, and one of those with a malignant schwannoma. The survival periods after operation were six, four, and eight months, respectively.

Details are given of one case: a two-year-old child with a sympathicoblastoma which had metastasized to the cervical glands on the same side as the tumour. In view of these metastases, it was decided that surgery was not indicated. Five years later there has been complete regression of the glandular metastases, and a reduction in the size of the primary tumour which is also becoming calcified.

Prednisone in cœliac disease.—Although a gluten-free diet controls most cases of cœliac disease, C. Zunin and G. Vallarino recommend that one of the cortisone group of steroids should also be used in severe cases, especially those with repeated crises which may prove dangerous to life. They give details of three cases in which the administration of prednisone resulted not only in the rapid amelioration of symptoms and signs, but also allowed the patients to take a diet containing gluten. They admit that the rationale for the use of steroids in this condition is not clear, but suggest that there may be an allergic factor which is controlled by prednisone.

Dexamethasone in rheumatoid arthritis.—As a result of their experience with 25 cases of rheumatoid arthritis treated with dexamethasone for periods of up to a year, A. Robecchi and his colleagues express the opinion that the side-effects arising from the prolonged use of dexamethasone are neither rare nor negligible. In their experience increase in weight and gastro-intestinal disturbances are more common with dexamethasone than with other cortisone derivations. In severe cases they noted an increase in side-effects when patients who had been receiving prednisone or triamcinolone were switched on to dexamethasone. Fortunately, the side-effects of dexamethasone were seldom severe, and it was rarely necessary to suspend its administration. They therefore recommend that it should only be used when it is indispensable, and only in the smallest possible doses. Strict supervision of all cases is essential.

Burr cells in uræmia.—In 1949, Schwartz and Motto described a form of red blood cell which was said to be particularly common in the presence of impaired renal function. Because of its crenated shape, with blunt spiny projections along its edge, it became known as a burr cell. A. Marmont and his colleagues report a case of uræmia, in which these burr cells accounted for about 5% of the red cells. Because of the relatively severe degree of anæmia, the patient had originally been sent into hospital as a case of hypertension with probable pernicious anæmia. The cause of the burr cells is not known, but, according to the authors, their presence is diagnostic of toxic hæmolytic anæmia—and particularly of the anæmia associated with uræmia.

'Notes from the Continent' are produced in collaboration with the Editors of Bruxelles-Médical (*Belgium*), Le Concours Médical (*France*), Münchener Medizinische Wochenschrift (*Germany*), *and* Minerva Medica (*Italy*).

THE PRACTITIONER

Fifty Years Ago

'Life is one long process of getting tired'.—Samuel Butler: *Note Books. Life*, vii.

OCTOBER, 1909

THE opening article in this number, 'On Being Tired', is by Sir Lauder Brunton, Bt., M.D., F.R.C.P., F.R.S., Consulting Physician to St. Bartholomew's Hospital, and is illustrated by some delightfully descriptive diagrams, such as 'Energy and Fatigue', 'Attention, Interest, Eagerness, Excitement, Reflection', 'The Pharisee and the Publican'. Sir Lauder tells a curious

'Leckadaisical attitudes.'
Mr. Lecky in various attitudes.

story of the distinguished historian William Edward Hartpole Lecky, who had, 'as every reader of *Punch* knows, a large magnificent head, mounted upon a long neck and a willowy body. He found out that his circulation was not sufficiently strong to raise the blood to his brain in sufficient quantity for its functional activity in the upright position. A mutual friend informed me that he wrote his *History* lying upon the sofa. I was so much interested in the question that I asked Mr. Lecky himself. He told me that this was a mistake, that he did not lie down, but actually wrote kneeling on a sofa which had a large broad head to it. This served him for a writing table, and in this kneeling position he wrote all his works, the blood having thus to travel to his brain in a horizontal line, instead of upwards against the force of gravity as it would have had to do in the sitting position'.

Discussing the effect of posture in regard to mental activity, the writer mentions that 'Mark Twain's horse, which was so feeble that it seemed as if it wished to lean up against a post to think, is not alone in its peculiarities, for they are shared by some human beings'. This extremely readable article concludes: 'A very interesting problem may yet turn out to be the relationship between intestinal toxæmia and the statement which has been put into the mouth of the unemployable British workman, "I eats well, I drinks well, I sleeps well, but when I sees a job of work coming along, I'm all of a tremble" '.

F. J. Smith, M.D., F.R.C.P., Physician to the London Hospital, discusses 'Indigestion'—'perhaps, the commonest malady of which patients complain, and, being so common, it has suffered the inevitable fate of being subjected to the modern craze for analysis and division and sub-division into the minutest of varieties. . . . For the present purpose it is sufficient to say that it is the means by which a stomach gives its possessor due notice that the food which he has put into it is not suitable for the occasion'. On the subject of 'Diarrhœa and Constipation' Smith states: 'It may be taken as a paradoxical axiom that when a patient over 40 years of age complains, without apparent cause, of diarrhœa, he is probably suffering from serious rectal obstruction or from constipation; on the other hand, I have had a patient complain thus of diarrhœa, but on personal inspection of his stools I found them to consist of large well-formed (but frequent) motions owing to the fact that he was a gross feeder'.

Arthur Latham, M.D., Physician to St. George's Hospital, describes 'The Treatment of Lobar Pneumonia'; Wilfred Harris, M.D., F.R.C.P., Physician to Outpatients, and to the Department for Nervous Diseases, St. Mary's Hospital, deals with 'Headache'; Guthrie Rankin, M.D., F.R.C.P., Physician to the Dreadnought and Royal Waterloo Hospitals, discourses on 'Jaundice'; and Harry Campbell, M.D., F.R.C.P., Physician to the North-West London Hospital and to the West End Hospital for Nervous Diseases, takes as his subject 'The Common Cold'.

Other articles in this issue are on 'Neuralgia' by Purves Stewart; 'Pertussis or Hooping Cough' by J. Hugh Thursfield; 'Treatment of Bronchitis' by J. Charlton Briscoe; 'Boils and Carbuncles and their Treatment' by H. G. Adamson; 'The Operative Technic of Piles' by

J. H. Nicoll; and 'Common Diseases of the Hair' by Tom Robinson. The last-mentioned paper concludes: 'We are often astonished at the rapidity of the growth of the hair, after it has fallen as a result of the exanthemata, when the general health is restored. We must be careful not to claim the satisfactory result entirely for our remedies. Time has been the remedy. It is otherwise with the other forms of baldness. We can in many instances gain good results, but we must always remember that in cases of senile baldness, or the universal kind, we are without any remedy which will either produce a single hair from an atrophied papilla, or produce on any scalp a single hair papilla'.

According to 'Notes from Foreign Journals', 'Weill and Mouriquand have made successful use of the hydrochloride of morphine in several cases of whooping-cough complicated with spasm of the glottis. They prescribe .005 mg. (gr. $\frac{1}{12}$) of morphine hydrochloride in a warm enema, which is to be retained. The effect of the drug was not very noticeable upon the number of attacks, but was remarkable upon the frequency and the severity of the glottic spasms'. For the treatment of 'the neurasthenic headache' Lemoine and Gérard recommend 'the static electrical bath and effluviation when it is possible. The following ointment should be rubbed in behind the ears:—℞ Mentholis gr. iv, Paraffin. moll. 3v. Misce. Fiat unguentum. Two cachets containing the following should be taken during the day:—℞ Pulveris Valerianæ, Camphoræ ana gr. iij, "Methylene-blue" gr. iss, Pulveris Myristicæ gr. $\frac{3}{4}$'.

In a lecture on 'The Treatment of Furunculosis', 'Professor Robin remarked that, although furunculosis usually lasted for some months, it is possible by treating the patients methodically and with careful attention to cure them fairly quickly. A patient was shown in whom the attack had lasted for six months and who was covered with scars from boils. She had been in hospital for a fortnight and was fit for discharge. . . . Treatment must be local and general. . . . As a drink, the patient must take 1 to 2 litres (1¼ to 3½ pints) of ordinary tar-water during the day. . . . No fermented food, like cheese, must be eaten, and neither *charcuterie* nor fish'.

The large number of 'Original Communications' has left no space for 'Reviews of Books', 'Practical Notes', and 'Preparations, Inventions, etc.'.

W. R. B.

We are proud . . .

to be recognised insurance agents for the medical and dental professions and proud, too, of our record of service for well over half a century.

The foundation of this service is expert, unbiased advice which is available on any insurance problem—LIFE, PENSION, SICKNESS, MOTOR CAR, HOUSEHOLD, EDUCATION.

Premiums are, in most cases, subject to substantial rebates and *all* the Agency's surplus is donated to the medical and dental charities.

The Agency can also help in negotiating LOANS for the purchase of a House, Equipment, or a Motor Car.

Medical Insurance Agency, Ltd.

Chairman: James Fenton C.B.E., M.D., M.R.C.P. *General Manager:* A. N. Dixon, A.C.I.I.

B.M.A. HOUSE, TAVISTOCK SQUARE, LONDON, W.C.1

Telephone: EUSTON 6031 (9 *lines*)

Branches at: Birmingham - Bristol - Cardiff - Dublin - Edinburgh - Glasgow Leeds - Manchester - Newcastle - Southampton